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NEWS 3	JUL 28	EPFULL enhanced with additional legal status information from the epoline Register
NEWS 4	JUL 28	IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
NEWS 5	JUL 28	STN Viewer performance improved
NEWS 6	AUG 01	INPADOCDB and INPAFAMDB coverage enhanced
NEWS 7	AUG 13	CA/CAplus enhanced with printed Chemical Abstracts page images from 1967-1998
NEWS 8	AUG 15	CAOLD to be discontinued on December 31, 2008
NEWS 9	AUG 15	CAplus currency for Korean patents enhanced
NEWS 10	AUG 27	CAS definition of basic patents expanded to ensure comprehensive access to substance and sequence information
NEWS 11	SEP 18	Support for STN Express, Versions 6.01 and earlier, to be discontinued
NEWS 12	SEP 25	CA/CAplus current-awareness alert options enhanced to accommodate supplemental CAS indexing of exemplified prophetic substances
NEWS 13	SEP 26	WPIDS, WPINDEX, and WPIX coverage of Chinese and and Korean patents enhanced
NEWS 14	SEP 29	IFICLS enhanced with new super search field
NEWS 15	SEP 29	EMBASE and EMBAL enhanced with new search and display fields
NEWS 16	SEP 30	CAS patent coverage enhanced to include exemplified prophetic substances identified in new Japanese-language patents
NEWS 17	OCT 07	EPFULL enhanced with full implementation of EPC2000
NEWS 18	OCT 07	Multiple databases enhanced for more flexible patent number searching
NEWS 19	OCT 22	Current-awareness alert (SDI) setup and editing enhanced
NEWS 20	OCT 22	WPIDS, WPINDEX, and WPIX enhanced with Canadian PCT Applications
NEWS 21	OCT 24	CHEMLIST enhanced with intermediate list of pre-registered REACH substances

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

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FILE COVERS 1907 - 4 Nov 2008 VOL 149 ISS 19
FILE LAST UPDATED: 3 Nov 2008 (20081103/ED)

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=> s (NNRTI or "non nucleoside reverse transcriptase inhibitors" or nevirapine or delavirdine or efavirenz or TMC125 or TMC278 or capravirine or DPC083 or "calanolide A")
824 NNRTI
647 NNRTIS
1162 NNRTI
(NNRTI OR NNRTIS)
1004839 "NON"
36 "NONS"
1004867 "NON"
("NON" OR "NONS")
51469 "NUCLEOSIDE"
33687 "NUCLEOSIDES"
63754 "NUCLEOSIDE"
("NUCLEOSIDE" OR "NUCLEOSIDES")
254050 "REVERSE"
10335 "REVERSES"
263298 "REVERSE"
("REVERSE" OR "REVERSES")
38942 "TRANSCRIPTASE"
816 "TRANSCRIPTASES"
39096 "TRANSCRIPTASE"
("TRANSCRIPTASE" OR "TRANSCRIPTASES")

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        588041 "INHIBITORS"
           694 "NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS"
                 ("NON"(W)"NUCLEOSIDE"(W)"REVERSE"(W)"TRANSCRIPTASE"(W)"INHIBIT
                 ORS")
          2435 NEVIRAPINE
           794 DELAVIRDINE
          1881 EFAVIRENZ
            53 TMC125
            16 TMC278
            98 CAPRAVIRINE
            14 DPC083
           205 "CALANOLIDE"
            25 "CALANOLIDES"
           207 "CALANOLIDE"
                 ("CALANOLIDE" OR "CALANOLIDES")
      22698929 "A"
           190 "CALANOLIDE A"
                 ("CALANOLIDE"(W)"A")
L1        4321 (NNRTI OR "NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS" OR
               NEVIRAPINE OR DELAVIRDINE OR EFAVIRENZ OR TMC125 OR TMC278 OR
               CAPRAVIRINE OR DPC083 OR "CALANOLIDE A")

=> s l1 and tenofovir
          1079 TENOFOVIR
L2         432 L1 AND TENOFOVIR

=> s l2 and py<=2004
       25113462 PY<=2004
L3         102 L2 AND PY<=2004

=> s l3 and TCM278
             0 TCM278
L4           0 L3 AND TCM278

=> s l3 and combination
        572125 COMBINATION
        127477 COMBINATIONS
        671052 COMBINATION
                 (COMBINATION OR COMBINATIONS)
L5          38 L3 AND COMBINATION

=> d l5 1-38 ibib ab

L5   ANSWER 1 OF 38  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2007:386131  CAPLUS
DOCUMENT NUMBER:          147:314258
TITLE:                    Rapid selection of drug-resistant HIV-1 during the
                          first months of suppressive ART in treatment-naive
                          patients
AUTHOR(S):                Metzner, Karin J.; Allers, Kristina; Rauch, Pia;
                          Harrer, Thomas
CORPORATE SOURCE:         Institute of Clinical and Molecular Virology,
                          University of Erlangen-Nuremberg, Erlangen, Germany
SOURCE:                   AIDS (Hagerstown, MD, United States) (2004),
                          21(6), 703-711
                          CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER:                Lippincott Williams & Wilkins
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Objective: Efficient antiretroviral therapy (ART) of HIV-1 infection
     reduces the viral load to undetectable levels and restores the immune
```

system. However, therapy failure appears in a substantial fraction of patients and is mostly associated with the appearance of drug-resistant viruses. It is still not clear when the drug pressure leads to the earliest selection and appearance of drug-resistant HIV-1 populations. In this study, we wanted to determine whether drug-resistant viruses are already selected during viral decline within the first months of ART. Design and methods: Fifteen mostly chronically HIV-1 infected patients were included. None had received ART prior to this study. The selection of three key resistance mutations, L90M (protease), K103N and M184V (reverse transcriptase), were measured by allele-specific real-time PCR allowing us to track minority quasispecies with a discriminative power of 0.01-0.2%. Results: Drug-resistant HIV-1 variants were found in 7/15 patients (46.7%) prior to ART. Rapid selection of drug resistance was detected in six patients (40%) independent of the presence of drug-resistant HIV-1 prior to ART. The risk for the selection of drug resistant viruses was correlated with the time until viral load became undetectable (P = 0.02). Besides the proportional increment of drug-resistant viruses, we observed in two patients a quant. increase of this virus population while the total viral load decreased. Conclusions: Drug-resistant viruses can be selected and replicate even in the first weeks of suppressive ART, thus, intensification of ART during the initial treatment period should be considered and further evaluated in clin. studies.

L5 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1081801 CAPLUS
DOCUMENT NUMBER: 144:224
TITLE: Virological outcome of tenofovir plus abacavir-based regimens in previously HIV suppressed patients (recover study)
AUTHOR(S): Moreno, S.; Elias, M. J. Perez; Terron, J. A.; Antela, A.; Domingo, P.; Ribera, E.; Palacios, R.; Ocampo, A.; Quero, J. Hernandez; Barros, C.; Arazo, P.; Carmena, J.; Herranz, C. R.; Casado, J. L.; Sanchez de la Rosa, R.
CORPORATE SOURCE: The Recovery Study Team, Hospital Ramon y Cajal, Madrid, Spain
SOURCE: International AIDS Conference, 15th, Bangkok, Thailand, July 11-16, 2004 (2004), E710C0555/227-E710C0555/232. Monduzzi Editore: Bologna, Italy.
CODEN: 69HFOX; ISBN: 88-7587-065-9
DOCUMENT TYPE: Conference; (computer optical disk)
LANGUAGE: English
AB We have been conducting a study to identify the most frequent NRTI associated toxicities causing withdrawal from that drug. All patients with sustained viral load suppression when switching to any TDF+ABC-based regimens were subsequently analyzed. We have available data of the first 83 patients treated with TDF+ABC based-regimens who have reached 24w in one of the following regimens: TDF + ABC+ NRTI (n=29), TDF + ABC + NNRTI (n=25), TDF + ABC + PIs (rtv boosted or not) (n=20) and TDF + ABC + NRTI + PI or NNRTI (n=9). After 24w 84% (ITT) of these patients remained suppressed. Virol. success across the different combinations was: TDF + ABC + NRTI (72%) TDF + ABC + NNRTI (96%); TDF + ABC + PI (rtv boosted or not) (90%); TDF + ABC + NRTI + PI or NNRTI (89%). We concluded that in heavily pretreated patients with suppressed viremia, NRTI + TDF + ABC-based regimen showed lower efficacy than PI or NNRTI-based combinations.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:983611 CAPLUS
DOCUMENT NUMBER: 143:292527
TITLE: Bioavailability and improved delivery of alkaline pharmaceutical drugs
INVENTOR(S): Yu, Ruey J.; Van Scott, Eugene J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 792,273.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050196418	A1	20050908	US 2005-50434	20050204
US 20040214215	A1	20041028	US 2004-792273	20040304 <--
WO 2006084174	A2	20060810	WO 2006-US3917	20060206
WO 2006084174	A3	20071004		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.:

US 2004-792273	A2	20040304
US 2003-452557P	P	20030307
US 2005-50434	A	20050204

OTHER SOURCE(S): MARPAT 143:292527

AB Embodiments of the invention relate to a composition, a process of making the composition, and to the use of the composition The compns. include a mol. complex formed between an alkaline pharmaceutical drug and at least one selected from a hydroxy acid, a polyhydroxy acid, a related acid, a lactone, or combinations thereof. The compns. provide improved bioavailability and improved delivery of the drug into the cutaneous tissues. For example, diphenhydramine hydrochloride 29 g (0.1 mol) was dissolved in water and 5 N sodium hydroxide generating diphenhydramine free base. Gluconolactone 18 g (0.1 mol) was added to form a mol. complex of 0.1 mol diphenhydramine free base with 0.1 mol gluconic acid/gluconolactone. The solution thus obtained was used for various forms of topical formulations including oil-in-water creams, lotions, gels and solns.

L5 ANSWER 4 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:79028 CAPLUS
DOCUMENT NUMBER: 143:37772
TITLE: Pharmacokinetics of antiretrovirals in pregnant women
AUTHOR(S): Mirochnick, Mark; Capparelli, Edmund
CORPORATE SOURCE: Boston University School of Medicine, Boston, MA, USA
SOURCE: Clinical Pharmacokinetics (2004), 43(15), 1071-1087
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Antiretroviral treatment of HIV-infected pregnant women is widely used to prevent mother-to-child HIV transmission and as primary therapy of maternal HIV infection. The physiol. changes associated with pregnancy have a large impact on drug disposition, and changes in antiretroviral pharmacokinetics during pregnancy must be understood for these drugs to be used safely and effectively in pregnant women. Zidovudine and didanosine, two of the nucleoside reverse transcriptase inhibitors, demonstrate an increase in clearance and decrease in area under the concentration-time curve during pregnancy. The clin. significance of these changes is unknown due to the lack of a clear relationship between plasma concns. of nucleoside reverse transcriptase inhibitors and clin. effects. Pharmacokinetic parameters of lamivudine, stavudine and abacavir are not significantly changed during pregnancy. There are no data describing the effect of pregnancy on the pharmacokinetics of the other nucleoside/nucleotide analogs (zalcitabine, emtricitabine and tenofovir). Pregnancy does not appear to have a significant effect on the pharmacokinetics of the non-nucleoside reverse transcriptase inhibitor nevirapine and there are no data describing the pharmacokinetics of the other non-nucleoside reverse transcriptase inhibitors (efavirenz and delavirdine) during pregnancy. Reduced plasma concns. during pregnancy have been described for several of the protease inhibitors, including nelfinavir (with administration of 750mg three times daily), indinavir, saquinavir and Kaletra (a co-formulation of lopinavir and ritonavir). Plasma concns. equivalent to those in nonpregnant adults have been reported in pregnant women receiving nelfinavir at doses of 1250mg twice daily, and the addition of ritonavir to saquinavir greatly increases saquinavir exposure to therapeutic concns. in pregnant women. No pregnancy pharmacokinetic data are available for the newer protease inhibitors atazanavir and fosamprenavir, or with other dual protease inhibitor combinations that include low dose ritonavir to boost concns. of the coadministered protease inhibitor. Further investigations of antiretroviral pharmacol. during pregnancy, including protein binding studies, are urgently needed.
REFERENCE COUNT: 118 THERE ARE 118 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:78220 CAPLUS
DOCUMENT NUMBER: 142:156181
TITLE: Preparation of monoacylated betulin and dihydrobetulin derivatives and use thereof as an anti-HIV drug
INVENTOR(S): Allaway, Graham P.; Wild, Carl T.; Kashiwada, Yoshiki; Lee, Kuo-hsiung
PATENT ASSIGNEE(S): Panacos Pharmaceuticals, Inc., Japan; The University of North Carolina At Chapel Hill; Niigata University of Pharmacy and Applied Life Sciences
SOURCE: U.S. Pat. Appl. Publ., 18 pp., Cont.-in-part of U.S. Ser. No. 670,797.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050020548	A1	20050127	US 2004-870555	20040618

US 7365221 B2 20080429
US 20040131629 A1 20040708 US 2003-670797 20030926 <--
WO 2006002248 A1 20060105 WO 2005-US22085 20050620
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2002-413451P P 20020926
US 2003-670797 A2 20030926
US 2004-870555 A 20040618
OTHER SOURCE(S): CASREACT 142:156181; MARPAT 142:156181
AB Betulin and dihydrobetulin acyl derivs. I [R1 = (un)substituted C2-20-carboxyacyl; R2 = H, halogen, OH, OR3; R3 = (un)substituted C2-20-carboxyacyl; R4 = H, CPh3; the dashed line represents an optional double bond between C(20) and C(29); Z = CH2 (when dashed line = double bond), Me (when dashed line = single bond)] or their pharmaceutically acceptable salts according to the present invention have been found to have potent anti-HIV activity. Thus, dihydrobetulin hydrogen 3,3-dimethylsuccinate I [R1 = C(:O)CH2CMe2CO2H, R2 = R4 = H, dashed line = single bond, Z = Me] was prepared from betulin, via tritylation with Ph3CCl in DMF containing DMAP, acylation with 2,2-dimethylglutaric acid in pyridine containing DMAP, detritylation with catalytic pyridinium tosylate in EtOH/CH2Cl2 and hydrogention in EtOAc containing catalytic Pd/C. The bioactivity of I [R1 = C(:O)CH2CMe2CO2H, R2 = R4 = H, dashed line = single bond, Z = Me] was determined [anti-HIV activity: EC50 = 0.0017 μM; cytotoxicity IC50 = 26.99 μM; therapeutic index = 16160].
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:33009 CAPLUS
DOCUMENT NUMBER: 142:253522
TITLE: Tenofovir DF, a nucleotide reverse transcriptase inhibitor
AUTHOR(S): Cui, Lan; An, Fu-rong; Wang, Xiao-min
CORPORATE SOURCE: Renji Hospital, Shanghai Second Medical University, Shanghai, 200001, Peop. Rep. China
SOURCE: Zhongguo Xinyao Zazhi (2004), 13(11), 1054-1058
CODEN: ZXZHA6; ISSN: 1003-3734
PUBLISHER: Zhongguo Xinyao Zazhishe
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review. Tenofovir DF, a nucleotide reverse transcriptase inhibitor, is approved for treatment of HIV infection in USA and Europe. It has a greater inhibitory effect than tenofovir and shows a stronger synergistic activity in combination with zidovudine, amprenavir, nevirapine or delavirdine and shows a mild to moderate synergistic action when combined with nelfinavir or adefovir. The pharmacol. actions, pharmacokinetics, clin. trial and tolerance of tenofovir DF are reviewed in this article.

L5 ANSWER 7 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:13034 CAPLUS
DOCUMENT NUMBER: 142:403142
TITLE: Atazanavir for the treatment of human immunodeficiency virus infection
AUTHOR(S): Busti, Anthony J.; Hall, Ronald G., II; Margolis, David M.
CORPORATE SOURCE: Dep. of Pharm. Practice, Texas Tech Univ. Health Sci. Cent. Sch. of Pharm., Dallas, TX, 75216, USA
SOURCE: Pharmacotherapy (2004), 24(12), 1732-1747
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Atazanavir is the first once-daily protease inhibitor for the treatment of human immunodeficiency virus type 1 infection and should be used only in combination therapy, as part of a highly active antiretroviral therapy (HAART) regimen. In addition to being the most potent protease inhibitor in vitro, atazanavir has a distinct cross-resistance profile that does not confer resistance to other protease inhibitors. However, resistance to other protease inhibitors often confers clin. relevant resistance to atazanavir. Currently, atazanavir is not a preferred protease inhibitor for initial HAART regimens. In treatment-naive patients, atazanavir can be given as 400 mg/day. However, atazanavir should be pharmacol. boosted with ritonavir in treatment-experienced patients or when coadministered with either tenofovir or efavirenz. Patients who receive atazanavir experience similar rates of adverse events compared with patients receiving comparator regimens. An exception is an increased risk of asymptomatic hyperbilirubinemia, which is due to competitive inhibition of uridine diphosphate-glucuronosyltransferase 1A1. Although hyperbilirubinemia is a common adverse drug reaction of atazanavir therapy (22 - 47%), fewer than 2% of patients discontinue atazanavir therapy because of this adverse effect. Common adverse effects reported with atazanavir include infection, nausea, vomiting, diarrhea, abdominal pain, headache, peripheral neuropathy, and rash. Of significance, fewer abnormalities have been observed in plasma lipid profiles in patients treated with atazanavir compared with other protease inhibitor-containing regimens. As with other protease inhibitors, atazanavir is also a substrate and moderate inhibitor of the cytochrome P 450 (CYP) system, in particular CYP3A4 and CYP2C9. Clin. significant drug interactions include (but are not limited to) antacids, proton pump inhibitors, histamine type 2 receptor antagonists, tenofovir, diltiazem, irinotecan, simvastatin, lovastatin, St. John's wort, and warfarin. We conclude that atazanavir is a distinctively characteristic protease inhibitor owing to its in vitro potency, once-daily dosing, distinct initial resistance pattern, and infrequent association with metabolic abnormalities.

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1079564 CAPLUS
DOCUMENT NUMBER: 142:232412
TITLE: CADA, a novel CD4-targeted HIV inhibitor, is synergistic with various anti-HIV drugs in vitro
AUTHOR(S): Vermeire, Kurt; Princen, Katrien; Hatse, Sigrid; de Clercq, Erik; Dey, Kaka; Bell, Thomas W.; Schols, Dominique
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: AIDS (London, United Kingdom) (2004), 18(16), 2115-2125

CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To evaluate the anti-HIV-1 activity of the cyclotriazadisulfonamide CADA against primary isolates in vitro and the combination of CADA with approved anti-HIV drugs for potential synergy. Methods: Peripheral blood mononuclear cells (PBMC) were treated with CADA and infected with 16 different clin. isolates. After 8 days of infection, the median inhibitory concentration (IC50) was calculated from the p24 viral antigen content in the supernatant. MT-4 cells were infected with HIV-1NL4.3 and then cultured with CADA or other antiretroviral drugs (i.e., several reverse transcriptase, protease and entry inhibitors), alone and in combination. After 4 days, IC50 was determined for the various drugs in replicate assays. Anal. of combined effects was performed using the median effect principle (CalcuSyn; Biosoft). Results: The entry inhibitor CADA exerted a potent and consistent anti-HIV-1 activity against a wide range of R5, R5/X4 and X4 primary isolates in PBMC. From the two-drug studies, combination indexes showed synergy between CADA and reverse transcriptase inhibitors (zidovudine, stavudine, lamivudine, zalcitabine, didanosine, abacavir, tenofovir, nevirapine, delavirdine and efavirenz), and protease inhibitors (lopinavir, saquinavir, indinavir, nelfinavir, amprenavir and ritonavir). In addition, the combination of CADA with the gp41 fusion inhibitor T-20 (enfuvirtide), the CXCR4 antagonist AMD3100 and the gp120-specific interacting plant lectins from Galanthus nivalis (GNA) and Hippeastrum hybrid (HHA) also resulted in a synergistic inhibition. Conclusions: Compds. that can specifically downmodulate the CD4 receptor in PBMC have broad-spectrum anti-HIV activity against primary isolates and act synergistically when used in conjunction with currently available antiretroviral drugs. They deserve further study as potential candidate anti-HIV drugs.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1017459 CAPLUS
DOCUMENT NUMBER: 142:347750
TITLE: Pharmacologic perspectives for once-daily antiretroviral therapy
AUTHOR(S): Anderson, Peter L.
CORPORATE SOURCE: Department of Clinical Pharmacy, School of Pharmacy, University of Colorado Health Sciences Center, Denver, CO, 80262-0238, USA
SOURCE: Annals of Pharmacotherapy (2004), 38(11), 1924-1934
CODEN: APHRER; ISSN: 1060-0280
PUBLISHER: Harvey Whitney Books Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. OBJECTIVE: To contrast available once-daily antiretroviral agents and combinations of these agents from a clin. pharmacol. viewpoint. DATA SOURCES: Data were extracted from publications and major HIV conference proceedings cited in MEDLINE (1966-Mar. 2004) using the search terms antiretroviral therapy, combination therapy, once-daily therapy, and pharmacokinetics. Addnl. refs. were obtained from the bibliogs. of these sources. STUDY SELECTION AND DATA Extraction: Information pertaining to pharmacol. perspectives for once-daily antiretroviral agents was selected. DATA SYNTHESIS: Maximal and durable suppression of plasma

HIV RNA, the principal goal of therapy, depends on the intrinsic antiviral activity of the antiretroviral regimen. A favorable tolerability/toxicity profile is also fundamentally important. All once-daily agents exhibit some pharmacol. limitations or lack adequate long-term follow-up. Of available agents, efavirenz has a long and distinguished efficacy record, with reasonable safety and moderate tolerability. Lamivudine, and newer agents such as atazanavir (or atazanavir/ritonavir), emtricitabine, fosamprenavir/ritonavir, and tenofovir, may offer pharmacol. advantages in the current state of once-daily therapy. Important considerations exist for coadministering once-daily agents including drug-drug interactions, drug-food incompatibilities, and synergistic toxicities. Few controlled studies have compared once-daily regimens with conventional regimens. CONCLUSIONS: Progress has been made toward once-daily therapy, but more clin. experience with available agents is needed, including comparative studies of entirely once-daily regimens vs. conventional regimens. Limitations of currently available agents signify a need for improved antiretroviral utilization or new alternative agents.

REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1016008 CAPLUS
DOCUMENT NUMBER: 142:6507
TITLE: Preparation of naphthyridine integrase inhibitors
INVENTOR(S): Johns, Brian A.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004101512	A2	20041125	WO 2004-US14814	20040512 <--
WO 2004101512	A3	20050127		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1622615	A2	20060208	EP 2004-751959	20040512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2006528694	T	20061221	JP 2006-532973	20040512
US 20070142365	A1	20070621	US 2005-556311	20051110
PRIORITY APPLN. INFO.:			US 2003-470059P	P 20030513
			WO 2004-US14814	W 20040512

OTHER SOURCE(S): MARPAT 142:6507
AB The title compds. [I; R1 = H, halo, alkyl, etc.; R2 = cycloalkyl, (un)substituted aryl, heterocyclyl; A = heterocycle; Q = alkyl, O, CO, SO2, etc.] that are HIV integrase inhibitors and therefore are useful in

the inhibition of HIV replication, the prevention and/or treatment of infection by HIV, and in the treatment of AIDS and/or ARC, were prepared E.g., a multi-step synthesis of 7-(5-benzyl-4H-1,2,4-triazol-3-yl)-1,6-naphthyridin-8-ol, was given. The compds. I have anti-HIV activity in the range IC50 of 1-1000 nM. The pharmaceutical composition comprising the compound I is disclosed.

L5 ANSWER 11 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:996008 CAPLUS
DOCUMENT NUMBER: 141:388636
TITLE: Use of combinations of reverse transcriptase inhibitors and viral DNA polymerase inhibitors for the treatment of viral diseases
INVENTOR(S): Jahn, Gerhard; Schott, Herbert; Hamprecht, Klaus; Mikeler, Elfriede
PATENT ASSIGNEE(S): Eberhard-Karls-Universitat Tubingen Universitatsklinikum, Germany
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004098640	A1	20041118	WO 2004-EP4693	20040504 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10321905	A1	20041209	DE 2003-10321905	20030505 <--
EP 1644040	A1	20060412	EP 2004-730971	20040504
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
US 20060172997	A1	20060803	US 2005-265825	20051103

PRIORITY APPLN. INFO.: DE 2003-10321905 A 20030505
WO 2004-EP4693 W 20040504

AB The invention discloses the use of at least one reverse transcriptase inhibitor (RTI) in the production of a medicament for the treatment of viral diseases which are triggered by DNA-viruses. The medicament is used in combination with at least one viral DNA polymerase inhibitor, and the at least one RTI and the at least one DNA polymerase inhibitor are present in the form of separated compds.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:974871 CAPLUS
DOCUMENT NUMBER: 142:296342
TITLE: Delayed progression to AIDS in volunteers treated with long-term HIV-1 immunogen (REMUNE) therapy in Thailand
AUTHOR(S): Chantratita, W.; Sukeepaisarncharoen, W.; Chandeying,

V.; Kulpradist, S.; Na Ayudhtaya, B. Israngkura; Rugpao, S.; Sirawaraporn, W.; Boonshuyar, C.; Churdboonchart, V.

CORPORATE SOURCE: Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

SOURCE: HIV Medicine (2004), 5(5), 317-325
CODEN: HMIEAB; ISSN: 1464-2662

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To observe the long-term effects of an immune-based therapy HIV-1 Immunogen (REMUNE; Immune Response Corp., Carlsbad, CA, USA) as a first course of treatment designed to sustain the immune system and thus delay the initiation of therapy with antiretroviral drugs and/or delay disease progression. In this open-label, multi-institute extended phase II P2101B study, disease progression, CD4 and CD8 T-cell counts, HIV-1 RNA levels, and genotypic antiretroviral drug resistance were examined in 223 asymptomatic HIV-1-infected Thai volunteers receiving REMUNE every 12 wk over 132 wk. A subset of subjects was randomly selected by the physicians to receive antiretroviral drugs for 10 mo. Patients treated with REMUNE demonstrated a low rate of clin. disease progression (0.72 per 100 person-years), higher CD4 and CD8 T-cell counts, higher body weight before and after treatment in the same patient, and stable viral load with no serious adverse events. We found no genotypic evidence of drug resistance in subgroups of patients on REMUNE monotherapy or REMUNE plus antiretrovirals (ARTs). This Thai study, like previous US and European studies, confirms that therapeutic immunization of HIV-infected volunteers modifies disease progression, as evidenced by stabilization of CD4 and CD8 T-cell counts, body weight, and viral load. As the majority of asymptomatic patients demonstrated an objective response to immunization, this study suggests that REMUNE may be utilized prior to initiation of antiviral drug therapy when CD4 cell counts are still above the current ART guidelines. Further work should be carried out to examine its potential use in combination with ART to reduce the increasingly common occurrence of drug resistance.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:915862 CAPLUS

DOCUMENT NUMBER: 142:455993

TITLE: Emtricitabine/tenofovir disoproxil fumarate

AUTHOR(S): Dando, Toni M.; Wagstaff, Antona J.

CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.

SOURCE: Drugs (2004), 64(18), 2075-2082
CODEN: DRUGAY; ISSN: 0012-6667

PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The nucleoside analog reverse transcriptase inhibitor (RTI) emtricitabine and the nucleotide analog RTI tenofovir disoproxil fumarate (tenofovir DF) have each shown antiviral activity against a number of HIV clin. isolates and cell lines. HIV variants with reduced susceptibility to emtricitabine and tenofovir have been selected for in vitro and have also been isolated from patients receiving the agents. Low rates of these variants have been observed in patients experiencing virol. failure in large studies of emtricitabine- or tenofovir DF-containing therapy. • Co-formulated oral emtricitabine/tenofovir DF was bioequivalent to the two agents as sep. formulations in a pharmacokinetic trial in healthy volunteers. • There are no published data on the clin. antiviral efficacy of

co-formulated oral emtricitabine/tenofovir DF. However, each agent is effective in combination regimens with other drugs. Ongoing studies in antiretroviral-naive patients are evaluating the efficacy of the individual formulations given together in combination with efavirenz or lopinavir/ritonavir. In the latter trial, HIV RNA levels were reduced and CD4+ cell counts were increased at 24 and 48 wk. • Emtricitabine and tenofovir DF are generally well tolerated. Diarrhoea, nausea and vomiting were the most common adverse events reported with coadministered emtricitabine and tenofovir DF as sep. formulations, as part of combination therapy.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:703121 CAPLUS
DOCUMENT NUMBER: 141:207236
TITLE: Preparation of 1,1-dioxido-4H-1,2,4-benzothiadiazines as hepatitis C polymerase inhibitors and anti-infective agents
INVENTOR(S): Pratt, John K.; Betebenner, David A.; Donner, Pamela L.; Green, Brian E.; Kempf, Dale J.; McDaniel, Keith F.; Maring, Clarence J.; Stoll, Vincent S.; Zhang, Rong
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 278 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20040167123	A1	20040826	US 2003-699513		20031031 <--
PRIORITY APPLN. INFO.:			US 2002-423209P	P	20021101
			US 2003-461784P	P	20030410
			US 2003-489448P	P	20030723
			US 2003-509107P	P	20031006

OTHER SOURCE(S): MARPAT 141:207236

AB Title compds. I [wherein A = monocyclic or bicyclic ring selected from hetero/aryl, cycloalkyl, cycloalkenyl, heterocyclyl; R1 = H, (un)substituted cycloalkyl/cyclo/alkenyl, alkoxycarbonyl/alkoxy/aryl/arylsulfonyl/arylsulfanyl/carboxy/cyano/heteroaryl/alkyl, heterocyclyl, etc.; R2, R3 = independently H, cyano, halo, (un)substituted alkenyl, alkoxycarbonyl, alkyl, heteroaryl, etc.; CR2R3C = 5- or 6-membered ring selected from Ph, pyridinyl, pyrimidinyl, pyridazinyl, thienyl, furanyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, tetrazolyl, cyclopentyl, and cyclohexyl; R4 = OH and derivs., halo, NH2 and derivs., etc.; R5 = independently CN, NO2, (un)substituted alk(en/yn)yl, hetero/aryl, arylsulfonyl, heterocyclyl etc.; n = 0-4; their pharmaceutically acceptable salts, stereoisomers, or tautomers] were prepared as hepatitis C (HCV) polymerase inhibitors for treating related infections. Thus II was prepared by alkylation of III (preparation given) with tris(methylthio)methyl Me sulfate in AcOH, cyclization with 2-amino-4[(4-methoxymethoxy)methyl]thiophene-3-sulfonamide, deprotection, condensation with cyclopropanecarboxaldehyde, reduction with LiBH4. I inhibited HCV polymerase with IC50's in the range of 0.002 μM to 500 μM. I inhibited RNA replication with EC50 in the range of 0.002 μM to > 100 μM. I exhibited a cytopathic effect reduction with TC50's in the

range of 6.6 μM to > 100 μM.

L5 ANSWER 15 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:702399 CAPLUS
DOCUMENT NUMBER: 142:85913
TITLE: Simple linear model provides highly accurate genotypic predictions of HIV-1 drug resistance
AUTHOR(S): Wang, Kai; Jenwitheesuk, Ekachai; Samudrala, Ram; Mittler, John E.
CORPORATE SOURCE: Department of Microbiology, University of Washington, Seattle, WA, USA
SOURCE: Antiviral Therapy (2004), 9(3), 343-352
CODEN: ANTHFA; ISSN: 1359-6535
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Drug resistance is a major obstacle to the successful treatment of HIV-1 infection. Genotypic assays are used widely to provide indirect evidence of drug resistance, but the performance of these assays has been mixed. We used standard stepwise linear regression to construct drug resistance models for seven protease inhibitors and 10 reverse transcriptase inhibitors using data obtained from the Stanford HIV drug resistance database. We evaluated these models by hold-one-out expts. and by tests on an independent dataset. Our linear model out-performed other publicly available genotypic interpretation algorithms, including decision tree, support vector machine and four rules-based algorithms (HIVdb, VGI, ANRS and Rega) under both tests. Interestingly, our model did well despite the absence of any terms for interactions between different residues in protease or reverse transcriptase. The resulting linear models are easy to understand and can potentially assist in choosing combination therapy regimens.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:702398 CAPLUS
DOCUMENT NUMBER: 141:253767
TITLE: Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach
AUTHOR(S): Negredo, Eugenia; Molto, Jose; Munoz-Moreno, Jose Antonio; Pedrol, Enric; Ribera, Esteve; Viciana, Pompeyo; Galindo, M. Jose; Miralles, Celia; Burger, David; Fumaz, Carmina Rodriguez; Puig, Jordi; Gel, Silvia; Rodriguez, Eva; Videla, Sebastia; Ruiz, Lidia; Clotet, Bonaventura
CORPORATE SOURCE: Germans Trias i Pujol Hospital, 'Lluita Contra la SIDA' and 'Irsicaixa' Foundations, Badalona, Spain
SOURCE: Antiviral Therapy (2004), 9(3), 335-342
CODEN: ANTHFA; ISSN: 1359-6535
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To assess the efficacy and safety of a once-daily antiretroviral regimen in HAART-experienced subjects with long-lasting viral suppression. Methods: One-hundred-and-sixty-nine patients with chronically suppressed viral load (limit of detection <50 copies/mL) were recruited. Based on patient willingness to simplify treatment, 84 of them continued receiving their usual treatment (BID Group) and 85 switched to once-daily didanosine/tenofovir/nevirapine (QD Group) in a non-randomized fashion. Results: At week 48, the proportion of

patients with viral suppression in the QD and in the BID Group, resp., was 97 vs 100% in the per-protocol anal. (P=0.497), and 76 vs 86% for the intention-to-treat anal. (P=0.176). Nevertheless, CD4 count decreased in the QD Group, with a mean decline of 95 cells/mm3 (95% CI: 45-145). Twelve subjects in the QD Group (14%) discontinued treatment due to adverse events, mainly nevirapine-related hepatitis (6%). No significant differences regarding the rate of acute pancreatitis or peripheral neuropathy were observed between both groups. A significant improvement in the lipid profile was only seen in the QD Group. High levels of adherence were observed in both groups during follow-up, as well as a good quality of life. At week 48, a reduction in effort to take medication (P≤0.001) and an increment in the satisfaction with the treatment (P<0.001) was only seen in the QD group. No differences were observed in median nevirapine trough levels between patients on twice-daily nevirapine at baseline (4820 ng/mL) and subjects in the QD Group (6090 ng/mL, P=0.30). Conclusion: Treatment simplification to a once-daily antiretroviral regimen based on didanosine, tenofovir and nevirapine may be a valid approach in HIV-infected subjects with long-lasting viral suppression. Combination of standard doses of didanosine and tenofovir may have contributed to the CD4 cell decline observed with this QD regimen.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:701799 CAPLUS

DOCUMENT NUMBER: 141:225774

TITLE: Preparation of 2',3'-dideoxy and 2',3'-didehydro nucleoside analogs as prodrugs for treating viral infections, most notably HIV

INVENTOR(S): Cheng, Yung-chi; Tanaka, Hiromichi; Baba, Masanori

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 45 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040167096	A1	20040826	US 2004-781305	20040218 <--
AU 2004260630	A1	20050210	AU 2004-260630	20040218
CA 2514466	A1	20050210	CA 2004-2514466	20040218
WO 2005011709	A1	20050210	WO 2004-US4713	20040218
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
BR 2004007374	A	20060110	BR 2004-7374	20040218
EP 1653976	A1	20060510	EP 2004-775776	20040218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1777432	A	20060524	CN 2004-80010529	20040218
JP 2006528972	T	20061228	JP 2006-532288	20040218

IN 2005KN01553	A	20061027	IN 2005-KN1553		20050805
MX 2005PA08736	A	20051005	MX 2005-PA8736		20050817
ZA 2005006630	A	20060628	ZA 2005-6630		20050818
PRIORITY APPLN. INFO.:			US 2003-448554P	P	20030219
			WO 2004-US4713	W	20040218

OTHER SOURCE(S): CASREACT 141:225774; MARPAT 141:225774

AB Nucleosides I, wherein B is nucleobase; Z is O or CH2; R is H, OH, halo, alkyl substituents; R1 can be H, Me, alkenyl, alkynyl; R2 is H, acyl, alkyl, ether, phosphoethers; and 2',3'-didehydro nucleosides II where Z is O; and R3 can alkyl, alkenyl, alkynyl, halo, hydroxy, were prepared as prodrugs and antiviral agents. Thus, the synthesized 2',3'-dideoxy and didehydro nucleoside analogs were tested as potential antiviral, anti-HIV and anti-infective prodrugs as independent agents, or in combination with other agents. Specifically, didehydro nucleoside III was prepared and tested in vitro as potent anti-HIV-1 agent (EC50 = 0.25 ± 0.14) and as well less toxic (ID50 >256) as D4T, therefor has the potential as a new anti-HIV drug.

L5 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:682819 CAPLUS
DOCUMENT NUMBER: 142:168540
TITLE: New Nucleoside/Nucleotide Backbone Options: A Review of Recent Studies
AUTHOR(S): Ruane, Peter J.; DeJesus, Edwin
CORPORATE SOURCE: West Hollywood, CA, USA
SOURCE: JAIDS, Journal of Acquired Immune Deficiency Syndromes (2004), 37(Suppl. 1), S21-S29
CODEN: JJASFJ; ISSN: 1525-4135
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) class continues to serve as an important component of the standard of care for HIV infection. Combinations of dual NRTIs/NtRTIs with protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) remain the most commonly used regimens in clin. practice. In recent years, clin. outcomes data on previously novel NRTI/NtRTI backbone combinations have provided clinicians with new options to address potency, tolerability, and convenience of antiretroviral therapy. However, the tolerability, drug-drug interactions, and resistance profiles of specific regimens using new NRTI/NtRTI combinations must be weighed against the needs and preferences of individual patients. This review summarizes recent efficacy and safety data on emerging NRTI/NtRTI combination backbones, including tenofovir DF (TDF) with lamivudine (3TC), abacavir with 3TC, didanosine (ddI) with 3TC, ddI with emtricitabine (FTC), and TDF with FTC.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:580483 CAPLUS
DOCUMENT NUMBER: 141:167290
TITLE: Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral-naive patients. A 3-year randomized trial
AUTHOR(S): Gallant, Joel E.; Staszewski, Schlomo; Pozniak, Anton L.; DeJesus, Edwin; Suleiman, Jamal M. A. H.; Miller, Michael D.; Coakley, Dion F.; Lu, Biao; Toole, John J.; Cheng, Andrew K.; Myers, R. A.; Wolfe, P.;

Stryker, R.; Schneider, S.; Kooshian, G. S.; Ruane, P.; Letendre, S.; Lampiris, H.; Beall, G.; Witt, M.; Simon, G.; Timpone, J.; Sension, M.; Juba, P.; Hernandez, J.; Campo, R.; Yangco, B.; Pierone, G., Jr.; Stephens, J.; Kessler, H. A.; Berger, D.; Wheat, J.; Greenberg, R. N.; Hellinger, J.; Tashima, K.; Morris, A. B.; Clay, P. G.; Tebas, P.; Markowitz, M.; Wohl, D.; Jemsek, J. G.; Pegram, S.; Slater, L.; Santana, J. L.; Sepulveda-Arzola, G.; Morales, J. O.; West, T.; Brand, J. D.; Bellos, N. C.; Borucki, M.; Barnett, B. J.; Green, S. L.; Craven, P. C.; Casiro, A.; Cassetti, I.; Cahn, P.; Benetucci, J. A.; Pedro, R.; Hayden, R. L.; Madruga, J. V. R.; Uip, D. E.; Timerman, A.; Mendonca, J. S.; Lewi, D. S.; Schechter, M.; Koenig, E.; Vittecoq, D.; Troisvallets, D.; Livrozet, J. M.; Bouvet, E.; Salmon-Ceron, D.; Sereni, D.; Arasteh, K.; Plettenberg, A.; Weitner, L.; Jager, H.; Lazzarin, A.; Esposito, R.; Guaraldi, G.; Concia, E.; Clotet, B.; Gonzalez-Lahoz, J.; Pulido, F.; Rubio, R.; Lopez-Aldeguer, J.; Friedl, A.; Opravil, M.; De Ruiter, A.; Easterbrook, P.; Williams, I.; Chen, S.-S.; Isaacson, E.; Jaffe, H. S.; Lu, B.; Margot, N.; Rooney, J. F.; Sayre, J.; Tran, S.; Fliederbaum, P.; James, J.; Schmidt, A.; Uffelman, K.; Capone, P.; Mingione, C.; Sidi, A.; Holmstrom, T.; Rodriguez-Amaya, K.; Sandholdt, I.

CORPORATE SOURCE: 903 Study Group, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD, USA

SOURCE: JAMA, the Journal of the American Medical Association (2004), 292(2), 191-201
CODEN: JAMAAP; ISSN: 0098-7484

PUBLISHER: American Medical Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Tenofovir disoproxil fumarate (DF) is a once-daily nucleotide analog reverse transcriptase inhibitor. The aim of this study was to evaluate the efficacy and safety of tenofovir DF compared with stavudine in antiretroviral-naive patients. A prospective, randomized, double-blind study conducted at 81 centers in the United States, South America, and Europe from June 9, 2000, to Jan. 30, 2004. A total of 753 patients infected with HIV who were antiretroviral naive were screened and 602 patients entered the study. Patients were randomized to receive either tenofovir DF (n=299) or stavudine (n=303), with placebo, in combination with lamivudine and efavirenz. The main outcome measure was the proportion of patients with HIV RNA levels of less than 400 copies/mL at week 48. In the primary intent-to-treat anal. in which patients with missing data or who added or switched antiretroviral medications before week 48 were considered as failures, the proportion of patients with HIV RNA of less than 400 copies/mL at week 48 was 239 (80%) of 299 in patients receiving tenofovir DF and 253 (84%) of 301 in patients receiving stavudine (95% confidence interval, -10.4% to 1.5%), exceeding the predefined -10% limit for equivalence. However, equivalence was demonstrated in the secondary analyses (HIV RNA <50 copies/mL) at week 48 and through 144 wk. Virol. failure was associated most frequently with efavirenz and lamivudine resistance. Through 144 wk, the K65R mutation emerged in 8 and 2 patients in the tenofovir DF and stavudine groups, resp. (P=.06). A more favorable mean change from baseline in fasting lipid profile was noted in the tenofovir DF group at week 144: for triglyceride levels (+1 mg/dL for tenofovir DF [n = 170] vs. +134 mg/dL for stavudine [n

= 162], P<.001), total cholesterol (+30 mg/dL [n = 170] vs. +58 mg/dL [n = 162], P<.001), direct low-d. lipoprotein cholesterol (+14 mg/dL [n=169] vs. +26 mg/dL [n=161], P<.001), and high-d. lipoprotein cholesterol (+9 mg/dL [n= 168] vs. +6 mg/dL [n=154], P=.003). Investigator-reported lipodystrophy was less common in the tenofovir DF group compared with stavudine group(9 [3%] of 299 vs. 58 [19%] of 301, P<.001). The number of bone fractures and the renal safety profile were similar between the 2 groups. Through 144 wk, the combination of tenofovir DF, lamivudine, and efavirenz was highly effective and comparable with stavudine, lamivudine, and efavirenz in antiretroviral-naive patients. However, tenofovir DF appeared to be associated with better lipid profiles and less lipodystrophy.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:522002 CAPLUS
DOCUMENT NUMBER: 141:133603
TITLE: Tenofovir treatment in an unselected cohort of highly antiretroviral experienced HIV positive patients
AUTHOR(S): Lerbaek, Anne; Kristiansen, Thomas B.; Katzenstein, Terese L.; Mathiesen, Lars; Gerstoft, Jan; Nielsen, Claus; Larsen, Klaus; Nielsen, Jens O.; Obel, Niels; Laursen, Alex L.; Nielsen, Susanne D.
CORPORATE SOURCE: Department of Infectious Diseases, Hvidovre Hospital, Copenhagen, Den.
SOURCE: Scandinavian Journal of Infectious Diseases (2004), 36(4), 280-286
CODEN: SJIDB7; ISSN: 0036-5548
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study explored the effect of tenofovir as implemented in clin. practice. Data are presented on 34 patients. Eleven patients had tenofovir added to a stable antiretroviral treatment (ART) and 23 patients had drugs other than tenofovir. CD4 counts, HIV-RNA levels and genotypic resistance were determined before and after 3 and 6 mo. After initiation of tenofovir treatment, a mean decrease in HIV-RNA for all 34 patients was observed (-0.43 log10 copies/mL and -0.49 log10 copies/mL after 3 and 6 mo, resp.). However, the effect of tenofovir on HIV-RNA in the group of patients who had tenofovir added to a stable ART was limited, and the decrease in HIV-RNA was higher in patients who had drugs other than tenofovir changed as well. After initiation of tenofovir treatment, no significant increases in CD4 count were observed All mutations associated with new nucleotide reverse transcriptase inhibitors could be explained by the background treatment. In conclusion, there was a significant decrease in HIV-RNA only when tenofovir was prescribed, in conjunction with other anti.retroviral drugs, to patients on a failing highly active antiretroviral drug regimen.

L5 ANSWER 21 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:515487 CAPLUS
DOCUMENT NUMBER: 141:71555
TITLE: Preparation of nitrogen-containing heterocyclic compounds as CXCR4 regulators
INVENTOR(S): Habashita, Hiromu; Kokubo, Masaya; Shibayama, Shiro; Tada, Hideaki; Tanihiro, Tatsuya
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 641 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004052862	A1	20040624	WO 2003-JP15718	20031209 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003288994	A1	20040630	AU 2003-288994	20031209 <--
EP 1571146	A1	20050907	EP 2003-778753	20031209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 20070167459	A1	20070719	US 2005-538758	20050610

PRIORITY APPLN. INFO.:
JP 2002-357446 A 20021210
JP 2003-162706 A 20030606
WO 2003-JP15718 W 20031209

OTHER SOURCE(S): MARPAT 141:71555

AB Compds. such as pyrimidine and quinazoline derivs. represented by the following general formulas (I) and (II), salts thereof, N-oxides thereof, solvates thereof or prodrugs of the same (wherein the ring A represents an optionally substituted nitrogen-containing heterocycle; the ring B represents an optionally substituted homocycle or an optionally substituted heterocycle; Y represents an optionally substituted hydrocarbyl group, an optionally substituted heterocyclic group, an optionally protected amino group, an optionally protected hydroxyl group or an optionally protected mercapto group; and T represents the ring A or an optionally substituted amino group) are prepared These compds. are CXCR4 regulators, in particular CXCR4 antagonists, and useful as preventives and/or remedies for various inflammatory diseases, immune diseases, various allergic diseases, infectious diseases, acquired immunodeficiency syndrome, infection with human immunodeficiency virus, psychiatric disorder, neurol. disease, cerebral diseases, cardiovascular diseases, metabolic diseases, or cancer, and agents for regeneration therapy, in particular transplant therapy. An assay system using SDF-1 which is an endogenous ligand of CXCR4 receptor, instead of HIV, was used in an assay for screening compds. which inhibit the binding of HIV to CXCR4 or CCR4 receptors on CD4-pos. cells. All the compds. prepared showed IC50 of 10 μM for inhibiting the binding of [125I]human SDF-1 to CEM cells, more specifically 0.1 μM for 2-(1-benzylpyrrolidin-3-ylamino)-4-(perhydroazepin-1-yl)pyrimidine. An ampule and tablet formulation containing 2-[[2-(dimethylamino)ethyl]amino]-4-(perhydroazepin-1-yl)pyrimidine were described.

L5 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:513490 CAPLUS
DOCUMENT NUMBER: 141:65057
TITLE: Dioxolane thymine and combinations for use against 3TC/AZT resistant strains of HIV
INVENTOR(S): Chu, Chung K.; Schinazi, Raymond F.
PATENT ASSIGNEE(S): The University of Georgia Research Foundation, Inc.,

	USA; Emory University
SOURCE:	PCT Int. Appl., 29 pp.
	CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004052296	A2	20040624	WO 2003-US39029	20031208 <--
WO 2004052296	A3	20040923		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2502625	A1	20040624	CA 2003-2502625	20031208 <--
AU 2003296360	A1	20040630	AU 2003-296360	20031208 <--
EP 1569659	A2	20050907	EP 2003-812874	20031208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003017113	A	20051025	BR 2003-17113	20031208
CN 1723025	A	20060118	CN 2003-80105479	20031208
US 20050209196	A1	20050922	US 2005-530088	20050401
MX 2005PA03637	A	20050816	MX 2005-PA3637	20050405
IN 2005KN00698	A	20060224	IN 2005-KN698	20050421
PRIORITY APPLN. INFO.:			US 2002-431812P P	20021209
			WO 2003-US39029 W	20031208

OTHER SOURCE(S): MARPAT 141:65057

AB The present invention relates to the use of a dioxolane thymine compound according to the chemical structure of Formula (I): where R1 is H, an acyl group, a C1-C20 alkyl or ether group, a phosphate, diphosphate, triphosphate or phosphodiester group, for use in the treatment of HIV infections which exhibit resistance to 3TC and/or AZT. Preferably, compds. according to the present invention are combined with at least one anti-HIV agent which inhibits HIV by a mechanism other than through the inhibition of thymidine kinase (TK). These agents include those selected from among nucleoside reverse transcriptase inhibitors (NRTI), non -nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, among others. These agents are generally selected from the group consisting of 3TC (Lamivudine), AZT (Zidovudine), (-)-FTC, ddI (Didanosine), ddC (zalcitabine), abacavir (ABC), tenofovir (PMPA), D-D4FC (Reverset), D4T (Stavudine), Racivir, L-D4FC, NVP (Nevirapine), DLV (Delavirdine), EFV (Efavirenz), SQVM (Saquinavir mesylate), RTV (Ritonavir), IDV (Indinavir), SQV (Saquinavir), NFV (Nelfinavir), APV (Amprenavir), LPV (Lopinavir), fuseon and mixts. thereof. The TK dependent agents, such as AZT and D4T, may be used in combination with one of the dioloxane thymine compds. according to the present invention, but the use of such agents may be less preferred. In preferred compns. according to the present invention, R1 is preferably H or a C2-C18 acyl group or a monophosphate group. Pharmaceutical compns. and methods of reducing the likelihood that a patient at risk for contract an HIV infection will contract the infection are other aspects of the present invention.

L5 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:469918 CAPLUS
DOCUMENT NUMBER: 141:46661
TITLE: Primer unblocking by HIV-1 reverse transcriptase and resistance to nucleoside RT inhibitors (NRTIs)
AUTHOR(S): Goldschmidt, Valerie; Marquet, Roland
CORPORATE SOURCE: IBMC, Unite Propre de Recherche 9002 du CNRS conventionnee a l'Universite Louis Pasteur, Strasbourg, 67084, Fr.
SOURCE: International Journal of Biochemistry & Cell Biology (2004), 36(9), 1687-1705
CODEN: IJBBFU; ISSN: 1357-2725
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. During zidovudine and stavudine treatment, HIV-1 selects several mutations (thymidine-associated mutations, TAMs) in the reverse transcriptase gene that confer high- and moderate-levels of resistance, resp., to these nucleoside reverse transcriptase inhibitors (NRTIs). The mechanism of the resistance provided by these mutations has long remained elusive. However, recent data showed that ATP-phosphorolysis, a reaction analogous to pyrophosphorolysis (the reverse of the nucleotide incorporation reaction) in which ATP is the pyrophosphate donor, is central to this mechanism by allowing repair of the chain-terminated primer. A detailed structural and mechanistic model accounting for the specificity of the ATP-phosphorolysis and its inhibition by the next complementary nucleotide is now available. In the context of multiresistant viruses, the TAMs are also associated with resistance to abacavir, and to a lesser extent to didanosine, zalcitabine and tenofovir. When associated with the TAMs, a dipeptide insertion in the fingers of reverse transcriptase increases the ATP-phosphorolysis of most chain terminators, stressing the increasing importance of this mechanism. However, some non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit this process. In addition, point mutations conferring resistance to NNRTIs (Y181C and L100I) or NRTIs (K65R, L74V, and M184V) partially resensitize the resistant viruses to AZT by inhibiting ATP-phosphorolysis. These findings allow rationalizing the benefic effects of some drug combinations and should contribute to improve drug cocktails. The development of NRTIs that would not allow the ATP-mediated excision to take place should prove beneficial for future treatments, even though high-level resistance to multiple NRTIs can ultimately develop in the absence of any significant primer unblocking.
REFERENCE COUNT: 156 THERE ARE 156 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:412943 CAPLUS
DOCUMENT NUMBER: 140:423711
TITLE: Preparation of 1,1-dioxido-4H-1,2,4-benzothiadiazines as hepatitis C polymerase inhibitors and anti-infective agents
INVENTOR(S): Pratt, John K.; Betebenner, David A.; Donner, Pamela L.; Green, Brian E.; Kempf, Dale J.; McDaniel, Keith F.; Maring, Clarence J.; Stoll, Vincent S.; Zhang, Rong
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 514 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004041818	A1	20040521	WO 2003-US34707	20031031 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20040097492	A1	20040520	US 2002-285714	20021101 <--
US 20040087577	A1	20040506	US 2003-410853	20030410 <--
US 20040162285	A1	20040819	US 2003-625121	20030723 <--
US 20050075331	A1	20050407	US 2003-679881	20031006
CA 2504385	A1	20040521	CA 2003-2504385	20031031 <--
AU 2003291670	A1	20040607	AU 2003-291670	20031031 <--
EP 1560827	A1	20050810	EP 2003-768559	20031031
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006509042	T	20060316	JP 2005-502238	20031031
BR 2003015897	A	20080513	BR 2003-15897	20031031
MX 2005PA04670	A	20050818	MX 2005-PA4670	20050429
IN 2005MN00522	A	20050930	IN 2005-MN522	20050531

PRIORITY APPLN. INFO.:			
US 2002-285714	A	20021101
US 2003-410853	A	20030410
US 2003-625121	A	20030723
US 2003-679881	A	20031006
WO 2003-US34707	W	20031031

OTHER SOURCE(S): MARPAT 140:423711

AB Title compds. I [wherein A = monocyclic or bicyclic ring selected from hetero/aryl, cycloalkyl, cycloalkenyl, heterocyclyl; R1 = H, (un)substituted cycloalkyl/cyclo/alkenyl, alkoxycarbonyl/alkoxy/aryl/arylsulfonyl/arylsulfanyl/carboxy/cyano/heteroaryl/alkyl, heterocyclyl, etc.; R2, R3 = independently H, cyano, halo, (un)substituted alkenyl, alkoxycarbonyl, alkyl, heteroaryl, etc.; CR2R3C = 5- or 6-membered ring selected from Ph, pyridinyl, pyrimidinyl, pyridazinyl, thienyl, furanyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, tetrazolyl, cyclopentyl, and cyclohexyl; R4 = OH and derivs., halo, NH2 and derivs., etc.; R5 = independently CN, NO2, (un)substituted alk(en/yn)yl, hetero/aryl, arylsulfonyl, heterocyclyl etc.; n = 0-4; their pharmaceutically acceptable salts, stereoisomers, or tautomers] were prepared as hepatitis C (HCV) polymerase inhibitors for treating related infections. Thus II was prepared by alkylation of III (preparation given) with tris(methylthio)methyl Me sulfate in AcOH, cyclization with 2-amino-4[(4-methoxymethoxy)methyl]thiphene-3-sulfonamide, deprotection, condensation with cyclopropanecarboxaldehyde, reduction with LiBH4. I inhibited HCV polymerase with IC50's in the range of 0.002 μM to 500 μM. I inhibited RNA replication with EC50 in the range of 0.002 μM to > 100 μM. I exhibited a cytopathic effect reduction with TC50's in the range of 6.6 μM to > 100 μM.

ACCESSION NUMBER: 2004:403774 CAPLUS
DOCUMENT NUMBER: 141:374319
TITLE: Molecular targets and compounds for anti-HIV therapy
AUTHOR(S): De Clercq, E.
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Biomedical and Health Research (2002), 55(Drug Discovery and Design), 272-278
CODEN: BIHREN; ISSN: 0929-6743
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Virtually all the compds. that are currently used, or under advanced clin. trial, for the treatment of HIV infections, belong to one of the following classes: (i) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs): i.e., zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir (ABC), emtricitabine [(-)FTC], tenofovir (PMPA) disoproxil fumarate; (ii) non -nucleoside reverse transcriptase inhibitors (NNRTIs): i.e., nevirapine, delavirdine, efavirenz, emivirine (MKC-442); and (iii) protease inhibitors (PIs): i.e., saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, and lopinavir. In addition to the reverse transcriptase and protease step, various other events in the HIV replicative cycle are potential targets for chemotherapeutic intervention: (i) viral adsorption, through binding to the viral envelope glycoprotein gp120 (polysulfates, polysulfonates, polyoxometalates, zintevir, neg. charged albumins, cosalane analogs); (ii) viral entry, through blockade of the viral coreceptors CXCR4 and CCR5 [bicyclams (i.e. AMD3100), polyphemusins (T22), TAK-779, MIP-1α LD78β isoform]; (iii) virus-cell fusion, through binding to the viral glycoprotein gp41 [T-20 (DP-178), T-1249 (DP-107), siamycins, betulinic acid derivs.]; (iv) viral assembly and disassembly, through NCp7 zinc finger-targeted agents [2,2'-dithiobisbenzamides (DIBAs), azadicarbonamide (ADA) and NCp7 peptide mimics]; (v) proviral DNA integration, through integrase inhibitors such as L-chicoric acid and diketo acids (i.e. L-731,988); (vi) viral mRNA transcription, through inhibitors of the transcription (transactivation) process (fluoroquinolone K-12, Streptomyces product EM2487, temacrazine, CGP64222). Also, in recent,years new NRTIs, NNRTIs and PIs have been developed that possess resp. improved metabolic characteristics (i.e. phosphoramidate and cyclosaligenyl pronucleotides of d4T), or increased activity against NNRTI-resistant HIV strains [second generation NNRTIs, such as capravirine and the novel quinoxaline, quinazolinone, Ph Et thiazoly-lthiourea (PETT) and emivirine (MKC-442) analogs], or, as in the case of PIs, a different, non-peptidic scaffold [i.e. cyclic urea (DMP 450), 4-hydroxy-2-pyrone (tipranavir)]. Given the multitude of mol. targets with which anti-HIV agents can interact, one should be cautious in extrapolating from cell-free enzymic assays to the mode of action of these agents in intact cells. A number of compds. (i.e. zintevir and L-chicoric acid, on the one hand, and CGP64222 on the other hand) have recently been found to interact with virus-cell binding and viral entry in contrast to their proposed modes of action targeted at the integrase and transactivation process, resp.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:363049 CAPLUS
DOCUMENT NUMBER: 142:15
TITLE: Antiviral drugs in current clinical use
AUTHOR(S): De Clercq, Erik

CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Journal of Clinical Virology (2004), 30(2), 115-133
CODEN: JCVIFB; ISSN: 1386-6532
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The current armamentarium for the chemotherapy of viral infections consists of 37 licensed antiviral drugs. For the treatment of human immunodeficiency virus (HIV) infections, 19 compds. have been formally approved: (i) the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine; (ii) the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir disoproxil fumarate; (iii) the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine and efavirenz; (iv) the protease inhibitors saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir (combined with ritonavir at a 4/1 ratio) and atazanavir; and the viral entry inhibitor enfuvirtide. For the treatment of chronic hepatitis B virus (HBV) infections, lamivudine as well as adefovir dipivoxil have been approved. Among the anti-herpesvirus agents, acyclovir, valaciclovir, penciclovir (when applied topically), famciclovir, idoxuridine and trifluridine (both applied topically) as well as brivudin are used in the treatment of herpes simplex virus (HSV) and/or varicella-zoster virus (VZV) infections; and ganciclovir, valganciclovir, foscarnet, cidofovir and fomivirsen (the latter upon intravitreal injection) have proven useful in the treatment of cytomegalovirus (CMV) infections in immunosuppressed patients (i.e. AIDS patients with CMV retinitis). Following amantadine and rimantadine, the neuraminidase inhibitors zanamivir and oseltamivir have recently become available for the therapy (and prophylaxis) of influenza virus infections. Ribavirin has been used (topically, as aerosol) in the treatment of respiratory syncytial virus (RSV) infections, and the combination of ribavirin with (pegylated) interferon-alpha has received increased acceptance for the treatment of hepatitis C virus (HCV) infections.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:350734 CAPLUS
DOCUMENT NUMBER: 140:417323
TITLE: Unexpected CD4 cell count decline in patients receiving didanosine and tenofovir-based regimens despite undetectable viral load
AUTHOR(S): Negredo, Eugenia; Molto, Jose; Burger, David; Viciana, Pompeyo; Ribera, Esteve; Paredes, Roger; Juan, Manel; Ruiz, Lidia; Puig, Jordi; Pruvost, Alain; Grassi, Jacques; Masmitja, Elisabeth; Clotet, Bonaventura
CORPORATE SOURCE: Germans Trias i Pujol Hospital, Lluita contra la SIDA and 'Irsicaixa' Foundations, Barcelona, Spain
SOURCE: AIDS (London, United Kingdom) (2004), 18(3), 459-463
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: We recently observed a significant CD4 cell count decline in patients receiving didanosine (ddI) 400 mg, tenofovir (TDF) and nevirapine (NVP), despite virol. suppression. Methods: We

identified from our computerized patient database subjects who initiated combinations containing ddI and/or TDF for reasons other than virol. failure, including simplification or intolerance. Changes in total, CD4+ and CD8+ lymphocyte counts since the initiation of therapy were analyzed retrospectively. Plasma concentration of ddI was prospectively determined in eight of these patients receiving ddI 400 mg + TDF + NVP and 3 wk after a ddI dosage reduction Results: A total of 302 patients were studied. A significant decrease in CD4 and CD8 and in total lymphocyte counts was only seen in subjects receiving ddI standard dose + TDF-containing regimens, despite the maintenance of viral suppression. More than 50% of these patients showed a decline of more than 100 CD4 cells at 48 wk. In contrast, subjects not receiving ddI + TDF together experienced the expected progressive increase in CD4 T-cell counts. Plasma levels of ddI were elevated in all patients receiving the standard ddI dose + TDF. DdI plasma levels significantly decreased when patients weighting > 60 kg reduced ddI dose to 250 mg, achieving similar levels to those generated by ddI 400 mg without TDF. Conclusions: Co-administration of ddI at standard doses plus TDF appears to exert a deleterious effect on CD4 and CD8 counts. Although lymphocyte toxicity related to excessive ddI plasma levels could explain our findings, other mechanisms cannot be excluded. Pharmacokinetic data suggest ddI dose reduction when coadministered with TDF.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 28 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:333850 CAPLUS

DOCUMENT NUMBER: 140:355836

TITLE: High-mannose oligosaccharide cluster conjugated with immunogenic protein for use as HIV vaccines

INVENTOR(S): Wang, Lai-xi

PATENT ASSIGNEE(S): University of Maryland Biotechnology Institute, Off. of Research Admin./ Tech. Dev., USA

SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004033663	A2	20040422	WO 2003-US32496	20031014 <--
WO 2004033663	A3	20060316		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2504755	A1	20040422	CA 2003-2504755	20031014 <--
AU 2003282821	A1	20040504	AU 2003-282821	20031014 <--
EP 1572963	A2	20050914	EP 2003-774819	20031014
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 20050244424	A1	20051103	US 2005-531124	20050630
PRIORITY APPLN. INFO.:			US 2002-417764P P	20021011

WO 2003-US32496 W 20031014

AB The present invention relates to a constructed oligosaccharide cluster, optionally bonded to an immunogenic protein, that can be administered to a subject to induce an immune response for increasing production of 2G12 and/or used in assays as reactive sites for determining compds. that inactivate and/or bind the high-mannose oligosaccharide cluster. The high-mannose oligosaccharide cluster comprises ≥2 high-mannose oligosaccharides attached a scaffolding framework of monosaccharide, cyclic peptide, cyclic organic compound or 11-bis-maleimidetetraethyleneglycol. The high-mannose oligosaccharide that mimics high-mannose N-glycan of HIV-1 gp120 comprises Man9, Man8, Man7, Man6, Man5 or a combination thereof. The high-mannose oligosaccharide of the invention is derived from soybean agglutinin or chemical synthesized. The immunogenic protein is keyhole limpet hemocyanin, tetanus toxoid, diphtheria toxoid, bovine serum albumin, ovalbumin, thyroglobulin, myoglobin, cholera toxin β-subunit, Ig. and/or tuberculosis purified protein derivative Compns. comprising these clusters, methods of using these clusters and compns. are disclosed.

L5 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:95024 CAPLUS
DOCUMENT NUMBER: 141:218332
TITLE: HIV Type 1 Genotypic Resistance in a Clinical Database Correlates with Antiretroviral Utilization
AUTHOR(S): Kagan, Ron; Winters, Mark; Merigan, Thomas; Heseltine, Peter
CORPORATE SOURCE: Department of Infectious Diseases, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, 92690, USA
SOURCE: AIDS Research and Human Retroviruses (2004), 20(1), 1-9
CODEN: ARHRE7; ISSN: 0889-2229
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We established a database of HIV-1 reverse transcriptase (RT) and protease (PR) sequences and mutations to monitor the prevalence of antiretroviral drug resistance and mutational patterns in clin. samples submitted for testing to a major U.S. reference laboratory At the end of 1998, 80% of the clin. samples tested harbored HIV strains with genotypically predicted resistance to at least one antiretroviral (ARV) drug. By the third quarter of 2002, the frequency of genotypically predicted resistance declined to 65% of samples tested. The prevalence of both PR and nucleoside RT inhibitor resistance declined over this period, while an increase in resistance to non-nucleoside RT inhibitors was found. These genotypic results strongly correlated with a nationwide decrease in the prescription of PR and nucleoside RT inhibitors, and an increase in the prescription of non-nucleoside RT inhibitors over the time period. The increased number of strains that were genotypically sensitive to all classes of ARV probably indicates an increase in genotypic assay use in ARV-naive individuals, however, the trends and correlations in this data set were similar when evaluated after vve strains. Continued monitoring of ARV resistance prevalence, patterns, and utilization trends in clin. databases provides insight into the evolving relationship between clin. practice and ARV resistance.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 30 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:20509 CAPLUS
DOCUMENT NUMBER: 140:70986

TITLE: Antiviral regimens with once daily oral zidovudine for HIV infections
INVENTOR(S): Keller, Amy Lee; Paes, Dominic Joseph Vincent
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004002498	A1	20040108	WO 2003-US20048	20030625 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003247646	A1	20040119	AU 2003-247646	20030625 <--

PRIORITY APPLN. INFO.: US 2002-392670P P 20020627
WO 2003-US20048 W 20030625

AB The present invention is directed to methods for treating HIV infections by administering 3'-azido-3'deoxythymidine (zidovudine) in alternative dosing regimens, preferentially once daily. A clin. study of zidovudine 600 mg once daily vs. zidovudine 300 mg twice daily in therapy-naive HIV-infected patients provided evidence that zidovudine administered once daily had antiviral activity as monotherapy and was well tolerated.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 31 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:288959 CAPLUS
DOCUMENT NUMBER: 139:30239
TITLE: Determining the relative efficacy of highly active antiretroviral therapy
AUTHOR(S): Louie, Michael; Hogan, Christine; Di Mascio, Michele; Hurley, Arlene; Simon, Viviana; Rooney, James; Ruiz, Nancy; Brun, Scott; Sun, Eugene; Perelson, Alan S.; Ho, David D.; Markowitz, Martin
CORPORATE SOURCE: Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, USA
SOURCE: Journal of Infectious Diseases (2003), 187(6), 896-900
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Despite the clin. benefits of combination antiviral therapy, whether maximal antiviral potency has been achieved with current drug combinations remains unclear. We studied the first phase of decay of human immunodeficiency virus type 1 (HIV-1) RNA in plasma, one early indicator of antiviral activity, after the administration of a novel combination of lopinavir/ritonavir, efavirenz, tenofovir disoproxil fumarate, and lamivudine and compared it with that observed in matched cohorts treated with alternative combination

regimens. On the basis of these comparisons, we conclude that the relative potency of highly active antiretroviral therapy may be augmented by as much as 25%-30%. However, it is important to emphasize that further study is warranted to explore whether these early measurements of relative efficacy provide long-term virol. and clin. benefits. Nevertheless, we believe that optimal treatment regimens for HIV-1 have yet to be identified and that continued research to achieve this goal is warranted.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:81468 CAPLUS
DOCUMENT NUMBER: 138:147077
TITLE: Tenofovir: a nucleotide analog for the management of human immunodeficiency virus infection
AUTHOR(S): Antoniou, Tony; Park-Wyllie, Laura Y.; Tseng, Alice L.
CORPORATE SOURCE: Inner City Health/HIV Program, Toronto, ON, Can.
SOURCE: Pharmacotherapy (2003), Volume Date 2002, 23(1), 29-43
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Tenofovir disoproxil fumarate, an acyclic nucleotide analog of adenosine monophosphate, is the most recent addition to the antiretroviral arsenal. After conversion to tenofovir by diester hydrolysis, subsequent phosphorylation by cellular enzymes to form the active tenofovir diphosphate is necessary for antiretroviral activity. Preliminary data suggest that tenofovir is as safe and efficacious as stavudine when given in combination with lamivudine and efavirenz for the treatment of antiretroviral-naive patients. In antiretroviral-experienced patients, the addition of tenofovir to stable background antiretroviral therapy resulted in approx. a 0.6 log10 copies/mL reduction in viral load relative to placebo. Extended follow-up suggests that such virol. gains may be durable. In vitro, recombinant human immunodeficiency virus (HIV) expressing the K65R mutation showed a 3-4-fold increase in the 50% inhibitory concns. of tenofovir when compared with wild type. In vivo, this mutation thus far appears to occur infrequently and is associated with variable virol. responses. Response rates to tenofovir vary with the number and pattern of thymidine analog mutations present before starting treatment with this agent. Tenofovir appears to be a well-tolerated agent in patients who are heavily pretreated and who have advanced disease. The main adverse effects appear to be gastrointestinal in nature and include nausea, vomiting, and diarrhea. In animals, osteomalacia and nephrotoxicity have occurred with tenofovir at exposures much higher than those observed in humans. Although no patient had to discontinue therapy as a result of elevated creatinine levels or hypophosphatemia through 58 wk of treatment, the toxicities associated with long-term tenofovir therapy in humans are unknown. Concomitant administration of tenofovir and didanosine increases the area under the concentration-time curve of the latter by 44-60%; monitoring for signs and symptoms of didanosine toxicity is recommended. The approved dosage of tenofovir is 300 mg (one tablet) once/day with meals. Given the ease of administration and relative safety from the perspectives of adverse effects and drug interactions, tenofovir has the potential to assume a large role in the treatment of patients with HIV infection.
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:695941 CAPLUS
DOCUMENT NUMBER: 137:232453
TITLE: Preparation of substituted benzophenones as inhibitors of reverse transcriptase
INVENTOR(S): Chan, Joseph Howing
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 163 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070470	A2	20020912	WO 2002-US6037	20020228 <--
WO 2002070470	A3	20030306		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2439820	A1	20020912	CA 2002-2439820	20020228 <--
AU 2002254056	A1	20020919	AU 2002-254056	20020228 <--
AU 2002254056	B2	20050929		
EP 1363877	A2	20031126	EP 2002-723265	20020228 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
HU 2003003326	A2	20040128	HU 2003-3326	20020228 <--
BR 2002007752	A	20040323	BR 2002-7752	20020228 <--
CN 1494528	A	20040505	CN 2002-805882	20020228 <--
NZ 527864	A	20040528	NZ 2002-527864	20020228 <--
JP 2004525914	T	20040826	JP 2002-569791	20020228 <--
IN 2003KN01052	A	20050708	IN 2003-KN1052	20030819
ZA 2003006549	A	20041122	ZA 2003-6549	20030821 <--
NO 2003003857	A	20031027	NO 2003-3857	20030901 <--
MX 2003PA07883	A	20031204	MX 2003-PA7883	20030902 <--
US 20040122064	A1	20040624	US 2004-469104	20040205 <--
US 6995283	B2	20060207		
US 20060009651	A1	20060112	US 2005-223634	20050909

PRIORITY APPLN. INFO.:	US 2001-272953P	P	20010302
	WO 2002-US6037	W	20020228
	US 2004-469104	A3	20040205

OTHER SOURCE(S): MARPAT 137:232453

AB Title compds. I [R1 = ≥1 substituent chosen from halo, CF3, alkyl, aminoalkyl, alkoxy, CN, NO2, NH2, thioalkoxy, etc.; R2 = H, halo, alkyl, NO2, NH2, alkylamino, CF3, alkoxy; R3 = OH, halo, CF3, NO2, alkyl; R4 = sulfonamido, sulfonylimino, etc.;] were prepared For instance, 3,5-dichlorobromobenzene was metalated (MTBE, n-BuLi, -50°) and acylated with the N,2-dimethoxy-N-methyl-5-chlorobenzamide and the resulting benzophenone converted to II. II was converted to III in 5 steps. Polymorphic forms of sodium, choline, calcium, magnesium, ethanolamine and triethylamine salts of III were prepared and characterized. Oral bioavailability and solubility parameters were determined for III and polymorphic salt forms thereof. Compds. of the present invention have

anti-HIV activity and deliver compds. that have anti- HIV activity in the range IC50 = 1-1000 nM against wild type and mutant viruses.

L5 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:521462 CAPLUS
DOCUMENT NUMBER: 137:88442
TITLE: Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms
INVENTOR(S): Shanahan-Pendergast, Elisabeth
PATENT ASSIGNEE(S): Ire.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-IE1	20020102 <--
WO 2002053138	A3	20020919		
W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG				
AU 2002219472	A1	20020716	AU 2002-219472	20020102 <--
EP 1351678	A2	20031015	EP 2002-727007	20020102 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 20040092583	A1	20040513	US 2004-250535	20040102 <--
PRIORITY APPLN. INFO.:			IE 2001-2 A	20010102
			WO 2002-IE1 W	20020102

OTHER SOURCE(S): MARPAT 137:88442
AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immunodysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixture showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

L5 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:935354 CAPLUS
DOCUMENT NUMBER: 136:64094
TITLE: The use of synthetic, non-hormonal 21-aminosteroids, derivatives, metabolites, and precursors thereof in the treatment of viral infections
INVENTOR(S): Prendergast, Patrick Thomas
PATENT ASSIGNEE(S): Kotze, Gavin Salomon, S. Afr.
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001097749 A2 20011227 WO 2001-IB1101 20010622 <--
WO 2001097749 A3 20020523
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 2001074383 A 20020102 AU 2001-74383 20010622 <--
PRIORITY APPLN. INFO.: IE 2000-511 A 20000623
IE 2001-275 A 20010321
WO 2001-IB1101 W 20010622

AB The invention discloses the use of synthetic, non-hormonal 21-aminosteroids, derivs., metabolites, and precursors thereof in the treatment of viral infections, particularly hepatitis and retroviral infection by HIV. Synthetic non-hormonal 21-aminosteroids are disclosed for use in the prophylaxis and therapy of hepatitis viral infections. These compds. can be administered alone or in combination with conventional antiviral agents.

L5 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:923790 CAPLUS
DOCUMENT NUMBER: 136:53748
TITLE: Preparation of propenone derivatives as integrase inhibitors and synergistic medicinal compositions containing them and anti-retrovirus agents
INVENTOR(S): Sato, Akihiko
PATENT ASSIGNEE(S): Shionogi & Co., Ltd., Japan
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001096329	A1	20011220	WO 2001-JP4887	20010611 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001062733	A	20011224	AU 2001-62733	20010611 <--
CA 2410763	A1	20021128	CA 2001-2410763	20010611 <--
EP 1295879	A1	20030326	EP 2001-936940	20010611 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001011678	A	20030603	BR 2001-11678	20010611 <--
HU 2003001713	A2	20031128	HU 2003-1713	20010611 <--
HU 2003001713	A3	20050428		
US 20030171406	A1	20030911	US 2002-296475	20021125 <--
ZA 2002009673	A	20040420	ZA 2002-9673	20021128 <--
IN 2002CN01999	A	20050225	IN 2002-CN1999	20021204

MX 2002PA12160	A	20030425	MX 2002-PA12160		20021209 <--
NO 2002006013	A	20030213	NO 2002-6013		20021213 <--
PRIORITY APPLN. INFO.:			JP 2000-176844	A	20000613
			WO 2001-JP4887	W	20010611

OTHER SOURCE(S): MARPAT 136:53748

AB Described is a combination of an integrase inhibitor with an anti-retrovirus active substance and medicinal compns. containing the same as the active ingredients. The above integrase inhibitors are represented by formula A-CO-CH:(OH)-B [A = (un)substituted heteroaryl; B = (un)substituted heteroaryl or aryl; provided that compds. represented by A and/or B = (un)substituted indol-3-yl are excluded.], tautomers, prodrugs, or pharmaceutically acceptable salts thereof and prepared The anti-retrovirus active substances are zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, tenofovir, tenofovir disproxil, nevirapine, delavirdine, emivirine, loviride, efavirenz, trovirdine, capravirine, TIBO, talviraline, UC781, saquinavir, nelfinavir, ritonavir, indinavir, KNI-272, lopinavir, VX-478, VB-19026, BILA-2011-BS, A-77003, A-80987, DMP-323, and XM-450. Thus, a THF solution of 1.31 g 2-acetyl-5-(4-fluorobenzyl)furan (18 ML) was cooled, treated dropwise with a 1 M lithium trimethylsilylamide solution in THF (7.8 mL) at -70 to -65°, gradually warmed to -10°, cooled to -70°, treated with a THF solution of 2.99 g 1-trityl-1H-1,2,4-triazole-3-carboxylic acid Et ester (30 mL), gradually warmed to room temperature, and stirred for 1.5 h, followed by work-up and treatment of the product with a mixture of 1 M aqueous HCl and dioxane at 80° for 0.5 h, and further work-up, to give 1-[5-(4-fluorobenzyl)furan-2-yl]-3-hydroxy-3-(1H-1,2,4-triazol-3-yl)-2-propen-1-one (I). I and 1-[2-(4-fluorobenzyl)furan-3-yl]-3-hydroxy-3-(2H-tetrazol-5-yl)-2-propen-1-one showed IC50 of 0.53 and 0.32 μg/mL, resp., against HIV-1 integrase. I in combination of zidovudine, lamivudine, nevirapine, capravirine, or nelfinavir showed synergism for inhibiting HIV-1 in MT-4 cells.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:489223 CAPLUS
DOCUMENT NUMBER: 135:71256
TITLE: Phosphonoformate lipid analogs for the treatment of drug-resistant human immunodeficiency virus infection
INVENTOR(S): Hostetler, Karl Y.; Mellors, John W.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047511	A2	20010705	WO 2000-US35137	20001222 <--
WO 2001047511	A3	20011220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2395430	A1	20010705	CA 2000-2395430	20001222 <--
BR 2000016844	A	20020910	BR 2000-16844	20001222 <--
EP 1244459	A2	20021002	EP 2000-988322	20001222 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003518495	T	20030610	JP 2001-548106	20001222 <--
RU 2265439	C2	20051210	RU 2002-118614	20001222
ZA 2002005020	A	20030626	ZA 2002-5020	20020621 <--
MX 2002PA06491	A	20021129	MX 2002-PA6491	20020628 <--
US 20030207843	A1	20031106	US 2002-169432	20021030 <--
PRIORITY APPLN. INFO.:			US 1999-173610P	P 19991229
			US 2000-174425P	P 20000104
			WO 2000-US35137	W 20001222

OTHER SOURCE(S): MARPAT 135:71256

AB Methods are provided for treating HIV infection in a subject in need thereof which use lipid analogs of phosphonoformate-containing pharmaceutically active compds. Lipid analogs contemplated for use comprise phosphonoformates covalently linked (directly or indirectly through a linker mol.) to a substituted or unsubstituted alkylglycerol, alkylpropanediol, alkylethanediol, or related moiety. In particular, the invention provides methods for treating viral infections caused by viruses which have developed resistance to currently available antiviral agents, as well as methods comprising the use of invention compds. in combination with azidodeoxythymidine to minimize the selection of drug-resistant HIV variants during therapy.

L5 ANSWER 38 OF 38 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:445983 CAPLUS
DOCUMENT NUMBER: 136:303303
TITLE: Antiviral drugs: current state of the art
AUTHOR(S): De Clercq, E.
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Journal of Clinical Virology (2001), 22(1), 73-89
CODEN: JCVIFB; ISSN: 1386-6532
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The chemotherapy of virus infections has definitely come of age. There are now 15 antiviral agents that have been formally licensed for the treatment of human immunodeficiency virus infections (zidovudine, didanosine, zalcitabine, stavudine, Lamivudine, Abacavir, Nevirapine, Delavirdine, Efavirenz, Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Lopinavir) and several others, such as Tenofovir Disoproxil, Emtricitabine, Capravirine, Emivirine, T-20 (Pentafuside), and AMD3100 (bicyclam), are under clin. development. Lamivudine has been approved, and several other compds. (such as Adefovir Dipivoxil, Emtricitabine, and Entecavir) are under clin. development, for the treatment of hepatitis B virus infections. Among the anti-herpesvirus agents, Aciclovir, Valaciclovir, Penciclovir, Famciclovir, Idoxuridine, Trifluridine, and Brivudin are used in the treatment of herpes simplex virus and varicella-zoster virus infections, and Ganciclovir, Foscarnet, Cidofovir, Fomivirsen, and Maribavir (the latter in the developmental stage) are used in the treatment of cytomegalovirus infections. Following amantadine and Rimantadine, the neuraminidase inhibitors, Zanamivir and Oseltamivir, have now become available for the therapy and prophylaxis of influenza virus infections, and so is Ribavirin for the treatment of respiratory syncytial virus infections and the combination of Ribavirin with

interferon-α for the treatment of hepatitis C virus infections.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	155.66	157.97

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-30.40	-30.40

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 31, 2008 (20081031/UP).

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.14	159.11

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-30.40

FILE 'CAPLUS' ENTERED AT 14:57:26 ON 04 NOV 2008
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FILE COVERS 1907 - 4 Nov 2008 VOL 149 ISS 19
FILE LAST UPDATED: 3 Nov 2008 (20081103/ED)

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=> d his

(FILE 'HOME' ENTERED AT 14:33:35 ON 04 NOV 2008)

FILE 'CAPLUS' ENTERED AT 14:40:02 ON 04 NOV 2008
L1 4321 S (NNRTI OR "NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS" O

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L2          432 S L1 AND TENOFOVIR
L3          102 S L2 AND PY<=2004
L4            0 S L3 AND TCM278
L5           38 S L3 AND COMBINATION

     FILE 'STNGUIDE' ENTERED AT 14:45:49 ON 04 NOV 2008

     FILE 'CAPLUS' ENTERED AT 14:57:26 ON 04 NOV 2008

=> s TCM278
L6            0 TCM278

=> s L3 and TMC278
            16 TMC278
L7            1 L3 AND TMC278

=> d l7 1 ibib ab

L7   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2007:175576  CAPLUS
DOCUMENT NUMBER:          146:258964
TITLE:                    Method for augmentation of intraepithelial and
                          systemic exposure of therapeutic agents having
                          substrate activity for cytochrome p450 enzymes and
                          membrane efflux systems following vaginal and oral
                          cavity administration
INVENTOR(S):              Pauletti, Giovanni M.; Harrison, Donald C.; Desai,
                          Kishorkumar J.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 24pp., Cont.-in-part of U.S.
                          Ser. No. 208,209.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   12
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     US 20070036834        A1    20070215    US 2006-522126          20060915
     AU 765269             B2    20030911    AU 2001-54192           20010703 <--
     US 20030049302        A1    20030313    US 2002-226667          20020821 <--
     US 6982091            B2    20060103
     US 20060002966        A1    20060105    US 2005-208209          20050818
     AU 2006292507         A1    20070329    AU 2006-292507          20060915
     CA 2622746            A1    20070329    CA 2006-2622746         20060915
     WO 2007035515         A2    20070329    WO 2006-US36087         20060915
     WO 2007035515         A3    20070927
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
             KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN,
             MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
             RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
     EP 1948103            A2    20080730    EP 2006-824976          20060915
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         R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR
PRIORITY APPLN. INFO.:                       US 2001-315877P     P  20010829
                                             US 2002-226667      A1 20020821
                                             US 2005-208209      A2 20050818
                                             US 2005-717680P     P  20050915
                                             AU 1998-76976       A3 19980610
                                             WO 2006-US36087     W  20060915
AB   The present invention relates to a method for augmentation of epithelial
     concentration and systemic exposure of therapeutic agents having a substrate
     affinity for cytochrome P 450 enzymes and membrane efflux transporter
     systems by using a vaginal or buccal drug delivery compns. and/or devices.
     Specifically, the invention relates to a method for augmentation of
     intraepithelial concentration and/or systemic bioavailability for delivery of
     anti-viral and/or anti-cancer therapeutic agents having a substrate
     affinity for cytochrome P 450 enzymes and membrane efflux systems by using
     a vaginal or buccal drug delivery of these drugs into the systemic
     circulation by delivering such drug to a subject in need thereof vaginally
     or buccally in an especially formulated composition increasing the drug's
     bioavailability by providing means for increasing the drug solubility and
     permeability through the vaginal or buccal mucosa.


=>  d his

     (FILE 'HOME' ENTERED AT 14:33:35 ON 04 NOV 2008)

     FILE 'CAPLUS' ENTERED AT 14:40:02 ON 04 NOV 2008
L1          4321 S (NNRTI OR "NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS" O
L2           432 S L1 AND TENOFOVIR
L3           102 S L2 AND PY<=2004
L4             0 S L3 AND TCM278
L5            38 S L3 AND COMBINATION

     FILE 'STNGUIDE' ENTERED AT 14:45:49 ON 04 NOV 2008

     FILE 'CAPLUS' ENTERED AT 14:57:26 ON 04 NOV 2008
L6             0 S TCM278
L7             1 S L3 AND TMC278

=> s TMC278
L8          16 TMC278

=> d 1-16 ibib ab

L8   ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2008:1105815  CAPLUS
DOCUMENT NUMBER:         149:348777
TITLE:                   Protein and nucleotide sequences of engineered novel
                         variants HIV reverse transcriptase and anti-viral drug
                         design
INVENTOR(S):             Arnold, Edward; Bauman, Joseph; Das, Kalyan
PATENT ASSIGNEE(S):      Rutgers, The State University, USA
SOURCE:                  PCT Int. Appl., 113pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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WO 2008109785	A2	20080912	WO 2008-US56110	20080306

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2007-905168P P 20070306

AB The present invention provides engineered novel variants of human immunodeficiency virus reverse transcriptase (HIV-RT) capable of being expressed in large quantity and that with polymerase and RNase H activity in a form that facilitates crystallization and high resolution structure resolution following X-ray diffraction. The engineered variants of HIV reverse transcriptase is a primary target for anti-HIV agents. The present invention facilitates high resolution determination of RT in complexes with RT drugs and RT inhibitors, and provides methods for systematic generation of variants and for structure based identification and design of novel RT inhibitors.

L8 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:1057514 CAPLUS

TITLE: Crystal engineering of HIV-1 reverse transcriptase for structure-based drug design

AUTHOR(S): Bauman, Joseph D.; Das, Kalyan; Ho, William C.; Baweja, Mukta; Himmel, Daniel M.; Clark, Arthur D., Jr.; Oren, Deena A.; Boyer, Paul L.; Hughes, Stephen H.; Shatkin, Aaron J.; Arnold, Eddy

CORPORATE SOURCE: Center for Advanced Biotechnology and Medicine, Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ and NCI-Frederick Cancer Research and Development Center, Frederick, MD, USA

SOURCE: Nucleic Acids Research (2008), 36(15), 5083-5092
CODEN: NARHAD; ISSN: 0305-1048

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB HIV-1 reverse transcriptase (RT) is a primary target for anti-AIDS drugs. Structures of HIV-1 RT, usually determined at .apprx.2.5-3.0 Å resolution, are important for understanding enzyme function and mechanisms of drug resistance in addition to being helpful in the design of RT inhibitors. Despite hundreds of attempts, it was not possible to obtain the structure of a complex of HIV-1 RT with TMC278, a nonnucleoside RT inhibitor (NNRTI) in advanced clin. trials. A systematic and iterative protein crystal engineering approach was developed to optimize RT for obtaining crystals in complexes with TMC278 and other NNRTIs that diffract X-rays to 1.8 Å resolution Another form of engineered RT was optimized to produce a high-resolution apo-RT crystal form, reported here at 1.85 Å resolution, with a distinct RT conformation. Engineered RTs were mutagenized using a new, flexible and cost effective method called methylated overlap-extension ligation independent cloning. Our anal. suggests that reducing the solvent content, increasing lattice contacts, and stabilizing the internal low-energy conformations of RT are critical for

the growth of crystals that diffract to high resolution The new RTs enable rapid crystallization and yield high-resolution structures that are useful in designing/developing new anti-AIDS drugs.

L8 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:588457 CAPLUS
DOCUMENT NUMBER: 149:33912
TITLE: Ligandless Heck Coupling between a Halogenated Aniline and Acrylonitrile Catalyzed by Pd/C: Development and Optimization of an Industrial-Scale Heck Process for the Production of a Pharmaceutical Intermediate
AUTHOR(S): Schils, Didier; Stappers, Fred; Solberghe, Geoffrey; van Heck, Richard; Coppens, Michelle; Van den Heuvel, Dirk; Van der Donck, Peter; Callewaert, Tom; Meeussen, Frank; De Bie, Erika; Eersels, Kristof; Schouteden, Ellen
CORPORATE SOURCE: Johnson and Johnson Pharmaceutical Research and Development, API Development, a Division Janssen Pharmaceutica, Beerse, B-2340, Belg.
SOURCE: Organic Process Research & Development (2008), 12(3), 530-536
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 149:33912
AB The aniline derivative 4-H2N-3,5-Me2C6H2CH:CHCN (I) is a key building block of rilpivirine (TMC278), a new potent NNRTI compound under clin. evaluation. Here the development of a new synthesis of I based on a Heck coupling between 4-iodo-2,6-dimethylaniline and acrylonitrile using low loading of Pd/C (0.5 mol %) as catalyst is presented. This resulted in a process which has been successfully transferred into production on 2400 mol-scale (6000 L reactor).
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:194151 CAPLUS
DOCUMENT NUMBER: 148:302131
TITLE: Two-dimensional infrared spectra reveal relaxation of the nonnucleoside inhibitor TMC278 complexed with HIV-1 reverse transcriptase
AUTHOR(S): Fang, Chong; Baumann, Joseph D.; Das, Kalyan; Remorino, Amanda; Arnold, Eddy; Hochstrasser, Robin M.
CORPORATE SOURCE: Department of Chemistry, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2008), 105(5), 1472-1477
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The two nitrile groups at the wings of the nonnucleoside HIV-1 reverse transcriptase (RT) inhibitor TMC278 are both identified in high-sensitivity 2D IR spectroscopy expts. of the HIV-1 RT/TMC278 complex. The vibrational spectra indicate that the two arms of the inhibitor sense quite different environments within the hydrophobic pocket. The vibrational relaxation of the two arms are almost equal at 3 ps from model studies. The 2D IR spectra expose a significant distribution of nitrile frequencies that diffuse at equilibrium on ultrafast time scales ranging from hundreds of femtoseconds to tens of picoseconds.

The slow spectral diffusion of the cyanovinyl arm of the inhibitor is attributed to its interaction with the backbone and side chains in the hydrophobic tunnel. The results show that the inhibitor cyano modes lose memory of their structural configurations relative to the hydrophobic pocket within tens of picoseconds. The cross-peaks between the two arms of the drug are tentatively attributed to relaxation of the nitrile state with both arms excited.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:194150 CAPLUS

DOCUMENT NUMBER: 148:302130

TITLE: High-resolution structures of HIV-1 reverse transcriptase/TMC278 complexes: strategic flexibility explains potency against resistance mutations

AUTHOR(S): Das, Kalyan; Bauman, Joseph D.; Clark, Arthur D.; Frenkel, Yulia V.; Lewi, Paul J.; Shatkin, Aaron J.; Hughes, Stephen H.; Arnold, Eddy

CORPORATE SOURCE: Center for Advanced Biotechnology and Medicine, Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, NJ, 08854, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2008), 105(5), 1466-1471 CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB TMC278 is a diarylpyrimidine (DAPY) nonnucleoside reverse transcriptase inhibitor (NNRTI) that is highly effective in treating wild-type and drug-resistant HIV-1 infections in clin. trials at relatively low doses (.apprx. 25-75 mg/day). We have determined the structure of wild-type HIV-1 RT complexed with TMC278 at 1.8 Å resolution, using an RT crystal form engineered by systematic RT mutagenesis. This high-resolution structure reveals that the cyanovinyl group of TMC278 is positioned in a hydrophobic tunnel connecting the NNRTI-binding pocket to the nucleic acid-binding cleft. The crystal structures of TMC278 in complexes with the double mutant K103N/Y181C (2.1 Å) and L100I/K103N HIV-1 RTs (2.9 Å) demonstrated that TMC278 adapts to bind mutant RTs. In the K103N/Y181C RT/ TMC278 structure, loss of the aromatic ring interaction caused by the Y181C mutation is counterbalanced by interactions between the cyanovinyl group of TMC278 and the aromatic side chain of Y183, which is facilitated by an .apprx. 1.5 Å shift of the conserved Y183MDD motif. In the L1001/K103N RT/ TMC278 structure, the binding mode of TMC278 is significantly altered so that the drug conforms to changes in the binding pocket primarily caused by the L1001 mutation. The flexible binding pocket acts as a mol. "shrink wrap" that makes a shape complementary to the optimized TMC278 in wild-type and drug-resistant forms of HIV-1 RT. The crystal structures provide a better understanding of how the flexibility of an inhibitor can compensate for drug-resistance mutations.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:114684 CAPLUS

TITLE: High-resolution structures of HIV-1 reverse transcriptase/TMC278 complexes: Strategic

flexibility explains potency against resistance mutations

AUTHOR(S): Das, Kalyan; Bauman, Joseph D.; Clark, Arthur D., Jr.; Frenkel, Yulia V.; Lewi, Paul J.; Shatkin, Aaron J.; Hughes, Stpehen H.; Arnold, Eddy

CORPORATE SOURCE: Center for Advanced Biotechnology and Medicine and Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, NJ, 08854, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, Early Edition (2008), (Jan 29 2008), 1-6, 6 pp.
CODEN: PNASC8
URL: http://www.pnas.org/cgi/reprint/0711209105v1

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB TMC278 is a diarylpyrimidine (DAPY) nonnucleoside reverse transcriptase inhibitor (NNRTI) that is highly effective in treating wild-type and drug-resistant HIV-1 infections in clin. trials at relatively low doses (.apprx.25-75 mg/day). We have determined the structure of wild-type HIV-1 RT complexed with TMC278 at 1.8 Å resolution, using an RT crystal form engineered by systematic RT mutagenesis. This high-resolution structure reveals that the cyanovinyl group of TMC278 is positioned in a hydrophobic tunnel connecting the NNRTI-binding pocket to the nucleic acid-binding cleft. The crystal structures of TMC278 in complexes with the double mutant K103N/Y181C (2.1 Å) and L100I/K103N HIV-1 RTs (2.9 Å) demonstrated that TMC278 adapts to bind mutant RTs. In the K103N/Y181C RT/TMC278 structure, loss of the aromatic ring interaction caused by the Y181C mutation is counterbalanced by interactions between the cyanovinyl group of TMC278 and the aromatic side chain of Y183, which is facilitated by an .apprx.1.5 Å shift of the conserved Y183MDD motif. In the L100I/K103N RT/TMC278 structure, the binding mode of TMC278 is significantly altered so that the drug conforms to changes in the binding pocket primarily caused by the L100I mutation. The flexible binding pocket acts as a mol. "shrink wrap" that makes a shape complementary to the optimized TMC278 in wild-type and drug-resistant forms of HIV-1 RT. The crystal structures provide a better understanding of how the flexibility of an inhibitor can compensate for drug-resistance mutations.

L8 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:1467771 CAPLUS

DOCUMENT NUMBER: 148:85720

TITLE: Aqueous suspension of TMC278

INVENTOR(S): Baert, Lieven Elvire Colette; Dries, Willy Albert Maria Carlo; Schueller, Laurent Bruno; Francois, Marc Karel Jozef; Van Remoortere, Peter Jozef Maria

PATENT ASSIGNEE(S): Tibotec Pharmaceuticals Ltd., Ire.

SOURCE: PCT Int. Appl., 30pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007147882	A2	20071227	WO 2007-EP56230	20070622
WO 2007147882	A3	20080619		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.: EP 2006-115938 A 20060623

AB This invention concerns pharmaceutical compns. for administration via i.m. or s.c. injection, comprising micro- or nanoparticles of TMC278, suspended in an aqueous pharmaceutically acceptable carrier, and the use of such pharmaceutical compns. in the treatment and prophylaxis of HIV infection. Thus, nanosuspension was prepared containing TMC278 5 g, Pluronic F108 1.25 g,.

L8 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:1349744 CAPLUS

TITLE: Two-dimensional infrared spectra reveal relaxation of the nonnucleoside inhibitor TMC278 complexed with HIV-1 reverse transcriptase

AUTHOR(S): Fang, Chong; Bauman, Joseph D.; Das, Kalyan; Remorino, Amanda; Arnold, Eddy; Hochstrasser, Robin H.

CORPORATE SOURCE: Dep. Chem., Univ. Pennsylvania, Philadelphia, PA, 19104-6323, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, Early Edition (2007), (Nov 26 2007), 1-6, 6 pp.
CODEN: PNASC8
URL: http://www.pnas.org/cgi/reprint/0709320104v1

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB The two nitrile groups at the wings of the nonnucleoside HIV-1 reverse transcriptase (RT) inhibitor TMC278 are both identified in high-sensitivity 2D IR spectroscopy expts. of the HIV-1 RT/TMC278 complex. The vibrational spectra indicate that the two arms of the inhibitor sense quite different environments within the hydrophobic pocket. The vibrational relaxation of the two arms are almost equal at 3 ps from model studies. The 2D IR spectra expose a significant distribution of nitrile frequencies that diffuse at equilibrium on ultrafast time scales ranging from hundreds of femtoseconds to tens of picoseconds. The slow spectral diffusion of the cyanovinyl arm of the inhibitor is attributed to its interaction with the backbone and side chains in the hydrophobic tunnel. The results show that the inhibitor cyano modes lose memory of their structural configurations relative to the hydrophobic pocket within tens of picoseconds. The cross-peaks between the two arms of the drug are tentatively attributed to relaxation of the nitrile state with both arms excited.

L8 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:818022 CAPLUS

DOCUMENT NUMBER: 147:158460

TITLE: Use of TMC278 for the long-term treatment of HIV infection

INVENTOR(S): Baert, Lieven Elvire Colette; Kraus, Guenter; Van 'T Klooster, Gerben Albert Eleutherius

PATENT ASSIGNEE(S): Tibotec Pharmaceuticals Ltd., Ire.
SOURCE: PCT Int. Appl., 19pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007082922	A2	20070726	WO 2007-EP50516	20070119
WO 2007082922	A3	20070920		
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AU 2007206901	A1	20070726	AU 2007-206901	20070119
CA 2636436	A1	20070726	CA 2007-2636436	20070119
EP 1981506	A2	20081022	EP 2007-712053	20070119
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
IN 2008DN05461	A	20081024	IN 2008-DN5461	20080624
MX 200809347	A	20080730	MX 2008-9347	20080718
KR 2008085194	A	20080923	KR 2008-718888	20080731
PRIORITY APPLN. INFO.:			EP 2006-100677 A	20060120
			WO 2007-EP50516 W	20070119

AB The invention discloses the use of a parenteral formulation comprising an antivirally effective amount of TMC278, or a pharmaceutically acceptable acid-addition salt thereof, and a carrier, for the manufacture of a medicament for the treatment of a subject being infected with HIV, wherein the formulation is to be administered intermittently at a time interval of at least one week.

L8 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:525940 CAPLUS
DOCUMENT NUMBER: 147:166280
TITLE: Synthesis of novel diarylpyrimidine analogues of TMC278 and their antiviral activity against HIV-1 wild-type and mutant strains
AUTHOR(S): Mordant, Celine; Schmitt, Benoit; Pasquier, Elisabeth; Demestre, Christophe; Queguiner, Laurence; Masungi, Chantal; Peeters, Anik; Smeulders, Liesbeth; Bettens, Eva; Hertogs, Kurt; Heeres, Jan; Lewi, Paul; Guillemont, Jerome
CORPORATE SOURCE: Chemistry Department, Johnson & Johnson Pharmaceutical Research and Development, Val de Reuil, F-27106, Fr.
SOURCE: European Journal of Medicinal Chemistry (2007), 42(5), 567-579
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

OTHER SOURCE(S): CASREACT 147:166280

AB Novel diarylpyrimidines I (X = NH, NMe, O, S; R1 = H, Me, MeO; R2 = H, Cl, Me, Et, MeO, Me2CH), which represent next generation of non-nucleoside reverse transcriptase inhibitors, were synthesized and their activities against human immunodeficiency virus type I (HIV-1) were assessed. Modulations at positions 2 and 6 of the cyanovinyl-substituted Ph ring generated interesting derivs. of TMC278 displaying high potency against wild-type and mutant viruses compared to nevirapine and efavirenz. The pharmacokinetic profile of the most potent compds. I (X = NH; R1 = Me, MeO; R2 = Cl) was evaluated and compared with TMC278 now in phase II clin. trials.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:175576 CAPLUS

DOCUMENT NUMBER: 146:258964

TITLE: Method for augmentation of intraepithelial and systemic exposure of therapeutic agents having substrate activity for cytochrome p450 enzymes and membrane efflux systems following vaginal and oral cavity administration

INVENTOR(S): Pauletti, Giovanni M.; Harrison, Donald C.; Desai, Kishorkumar J.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 24pp., Cont.-in-part of U.S. Ser. No. 208,209.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 12

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070036834	A1	20070215	US 2006-522126	20060915
AU 765269	B2	20030911	AU 2001-54192	20010703
US 20030049302	A1	20030313	US 2002-226667	20020821
US 6982091	B2	20060103		
US 20060002966	A1	20060105	US 2005-208209	20050818
AU 2006292507	A1	20070329	AU 2006-292507	20060915
CA 2622746	A1	20070329	CA 2006-2622746	20060915
WO 2007035515	A2	20070329	WO 2006-US36087	20060915
WO 2007035515	A3	20070927		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
EP 1948103	A2	20080730	EP 2006-824976	20060915
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				

PRIORITY APPLN. INFO.: US 2001-315877P P 20010829
US 2002-226667 A1 20020821

US 2005-208209	A2	20050818
US 2005-717680P	P	20050915
AU 1998-76976	A3	19980610
WO 2006-US36087	W	20060915

AB The present invention relates to a method for augmentation of epithelial concentration and systemic exposure of therapeutic agents having a substrate affinity for cytochrome P 450 enzymes and membrane efflux transporter systems by using a vaginal or buccal drug delivery compns. and/or devices. Specifically, the invention relates to a method for augmentation of intraepithelial concentration and/or systemic bioavailability for delivery of anti-viral and/or anti-cancer therapeutic agents having a substrate affinity for cytochrome P 450 enzymes and membrane efflux systems by using a vaginal or buccal drug delivery of these drugs into the systemic circulation by delivering such drug to a subject in need thereof vaginally or buccally in an especially formulated composition increasing the drug's bioavailability by providing means for increasing the drug solubility and permeability through the vaginal or buccal mucosa.

L8 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2006:1065877 CAPLUS
DOCUMENT NUMBER:	145:389322
TITLE:	Intermittent administration of parenteral TMC278 for the prevention of HIV infection
INVENTOR(S):	Baert, Lieven Elvire Colette; Lewi, Paulus Joannes; Heeres, Jan
PATENT ASSIGNEE(S):	Tibotec Pharmaceuticals Ltd., Ire.
SOURCE:	PCT Int. Appl., 18pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006106103	A2	20061012	WO 2006-EP61303	20060404
WO 2006106103	A3	20070607		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
AU 2006231585	A1	20061012	AU 2006-231585	20060404
CA 2602231	A1	20061012	CA 2006-2602231	20060404
EP 1881848	A2	20080130	EP 2006-725539	20060404
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
JP 2008534651	T	20080828	JP 2008-504756	20060404
IN 2007DN05672	A	20070817	IN 2007-DN5672	20070723
KR 2008009051	A	20080124	KR 2007-719959	20070831
US 20080194601	A1	20080814	US 2007-910034	20070928
MX 200712277	A	20071017	MX 2007-12277	20071003
CN 101155599	A	20080402	CN 2006-80011429	20071008

PRIORITY APPLN. INFO.: EP 2005-102616 A 20050404
WO 2006-EP61303 W 20060404

AB The invention discloses the use of a parenteral formulation comprising the non-nucleoside reverse transcriptase inhibitor TMC278 for the long-term prevention of HIV infection in a subject at risk of being infected by HIV, which comprises the intermittent administration of the the formulation at long time intervals.

L8 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:855447 CAPLUS
DOCUMENT NUMBER: 145:448644
TITLE: Short-term antiviral activity of TMC278 - a novel NNRTI - in treatment-naive HIV-1-infected subjects
AUTHOR(S): Goebel, Frank; Yakovlev, Alexy; Pozniak, Anton L.; Vinogradova, Elena; Boogaerts, Griet; Hoetelmans, Richard; de Bethune, Marie-Pierre P.; Peeters, Monika; Woodfall, Brian
CORPORATE SOURCE: Ludwig-Maximilians University, Munich, Germany
SOURCE: AIDS (Hagerstown, MD, United States) (2006), 20(13), 1721-1726
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: To evaluate antiviral activity, pharmacokinetics, tolerability and safety of TMC278, a non-nucleoside reverse transcriptase inhibitor (NNRTI), when given as a 25, 50, 100 or 150 mg once-daily dose for 7 days to antiretroviral-naive HIV-infected subjects. Design: Randomized, double-blind, placebo-controlled, phase IIa clin. trial. Methods: Participants were 47 antiretroviral naive HIV-infected subjects. Primary outcome was the change in plasma HIV-1 RNA viral load from baseline to day 8. Secondary outcomes were evaluation of pharmacokinetics of TMC278, immunol. changes, safety and tolerability, and evolution of viral genotypic and phenotypic patterns. Results: Patients treated with TMC278 achieved a median decrease in plasma viral load from baseline of 1.199 log10 copies/mL compared with a 0.002 log10 copies/mL gain in the placebo group ($P < 0.01$). A significantly higher proportion of subjects in the TMC278 groups obtained a viral load decrease of > 1.0 log10 compared with the placebo group (25/36 vs. 0/11) ($P < 0.01$). No significant dose differences were noted in either antiviral effect or safety. No genotypic changes associated with antiretroviral resistance were detected between baseline and the end of the trial. Plasma concns. of TMC278 were above the target concentration (13.5 ng/mL) at all time points for all TMC278-treated subjects. The most common reported adverse event was headache (TMC278 14%; placebo 18%). Conclusions: TMC278 showed antiviral activity when given as monotherapy for 7 days at all doses studied and the drug was safe and well tolerated. Trials of longer treatment duration with TMC278, in combination with other antiretroviral drugs, are underway to assess the long-term durability of antiviral response, safety and tolerability.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:835787 CAPLUS
DOCUMENT NUMBER: 145:305388
TITLE: Aspects of successful drug discovery and development
AUTHOR(S): Pauwels, Rudi
CORPORATE SOURCE: Chemin de Layaz 3, Saint-Legier, CH-1806, Switz.

SOURCE: Antiviral Research (2006), 71(2-3), 77-89
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Despite landmark achievements (e.g. >20 new anti-HIV drugs), a number of important therapeutic challenges remain. Although an expanding array of new drug discovery technologies has become available, drug research and development (R&D) productivity in general is still low. The establishment of close functional links between specialists active in early discovery, development and the clinic can thereby contribute to overall efficiency and higher success rates of new drug candidates. One of the more qual. discovery challenges is to improve the predictability of early stage research models in term of in vivo drug efficacy. A cell-based model using viral replication in human T cells (MT-4) is used as an example from the HIV field to highlight the role of cell-based assays as tools for new target discovery, lead finding and optimization. The development of the next generation HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs) TMC125 and TMC278 and the protease inhibitor (PI) TMC114 (Prezista), further point to new fundamental strategies to combat and prevent antiviral drug resistance and to the importance of incorporating clin. and pharmaceutical aspects into lead finding and optimization, drug design and drug candidate selection. A more parallel-oriented drug discovery strategy is thus portrayed that harnesses some evolutionary' principles in combination with technologies that are currently rationalizing drug discovery.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:211282 CAPLUS
DOCUMENT NUMBER: 145:158757
TITLE: Next-generation HIV-1 non-nucleoside reverse transcriptase inhibitors
AUTHOR(S): Boone, Lawrence R.
CORPORATE SOURCE: Discovery Virology, GlaxoSmithKline, Research Triangle Park, NC, 27709, USA
SOURCE: Current Opinion in Investigational Drugs (Thomson Scientific) (2006), 7(2), 128-135
CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB This review discusses the desired attributes of a next-generation HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) and highlights the properties of compds. currently or recently in clin. development. TMC-125 is currently in phase III clin. trials and on track to become the first NNRTI suitable for use in NNRTI-experienced patients. TMC-278 is structurally related to TMC-125, but is more potent in vitro and has pharmacokinetics suitable for once-daily administration. It is currently undergoing phase II clin. trials. BILR-355 BS, a dipyridodiazepinone compound, is in early phase II clin. trials. It requires ritonavir as a booster and has reduced inhibitory activity against several key NNRTI-resistant HIV-1 strains. Development of the NNRTIs capravirine and GW-695634 has been discontinued because of lack of efficacy and safety issues, resp.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:216682 CAPLUS

DOCUMENT NUMBER: 142:273973
TITLE: Combinations of pyrimidine-containing nonnucleoside reverse transcriptase inhibitor (NNRTI) TMC278 with reverse transcriptase inhibitors for the treatment of HIV infection
INVENTOR(S): Stoffels, Paul
PATENT ASSIGNEE(S): Tibotec Pharmaceuticals Ltd., Ire.
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005021001	A1	20050310	WO 2004-EP52028	20040903
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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AU 2004268390	A1	20050310	AU 2004-268390	20040903
CA 2537095	A1	20050310	CA 2004-2537095	20040903
EP 1663240	A1	20060607	EP 2004-787096	20040903
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BR 2004014027	A	20061024	BR 2004-14027	20040903
JP 2007520443	T	20070726	JP 2006-525150	20040903
CN 101060844	A	20071024	CN 2004-80025426	20040903
EP 1632232	A1	20060308	EP 2005-108086	20050902
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AU 2005279157	A1	20060309	AU 2005-279157	20050902
AU 2005279158	A1	20060309	AU 2005-279158	20050902
CA 2577273	A1	20060309	CA 2005-2577273	20050902
CA 2577288	A1	20060309	CA 2005-2577288	20050902
WO 2006024667	A1	20060309	WO 2005-EP54341	20050902
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WO 2006024668	A1	20060309	WO 2005-EP54342	20050902
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            SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
            ZA, ZM, ZW
        RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
            IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
            CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
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            KG, KZ, MD, RU, TJ, TM
    US 20060111379        A1    20060525    US 2005-219163          20050902
    EP 1789139            A1    20070530    EP 2005-779369          20050902
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            IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL,
            BA, HR, MK, YU
    CN 101056673          A     20071017    CN 2005-80038025        20050902
    CN 101068597          A     20071107    CN 2005-80038093        20050902
    JP 2008511591         T     20080417    JP 2007-528885          20050902
    JP 2008511592         T     20080417    JP 2007-528886          20050902
    BR 2005014861         A     20080624    BR 2005-14861           20050902
    BR 2005014871         A     20080624    BR 2005-14871           20050902
    IN 2006DN00687        A     20070817    IN 2006-DN687           20060210
    US 20080200435        A1    20080821    US 2006-570228          20060228
    MX 2006PA02437        A     20060620    MX 2006-PA2437          20060302
    NO 2006001374         A     20060327    NO 2006-1374            20060327
    MX 200702594          A     20070425    MX 2007-2594            20070301
    MX 200702595          A     20070425    MX 2007-2595            20070301
PRIORITY APPLN. INFO.:                        EP 2003-103275      A   20030903
                                              US 2003-499771P     P   20030903
                                              EP 2003-103319      A   20030908
                                              EP 2003-103335      A   20030910
                                              EP 2003-103668      A   20031002
                                              US 2003-508486P     P   20031003
                                              EP 2001-203090      A   20010813
                                              EP 2002-77748       A   20020610
                                              WO 2002-EP8953      W   20020809
                                              US 2004-485636      A2  20040203
                                              MY 2004-3578        A   20040902
                                              EP 2004-52028       T0  20040903
                                              WO 2004-EP52028     W   20040903
                                              EP 2005-101447      A   20050225
                                              EP 2005-101467      A   20050225
                                              EP 2005-108086      A   20050902
                                              WO 2005-EP54341     W   20050902
                                              WO 2005-EP54342     W   20050902
AB   The invention discloses combinations of a pyrimidine-containing NNRTI named
     TMC278 [4-((4-((4-(2-cyanoethenyl)-2,6-dimethylphenyl)amino)-2-
     pyrimidinyl)amino)benzonitrile] with nucleoside reverse transcriptase
     inhibitors such as emtricitabine, lamivudine or abacavir and/or nucleotide
     reverse transcriptase inhibitors such as tenofovir useful for the
     treatment of HIV-infected patients or for the prevention of HIV
     transmission or infection.
REFERENCE COUNT:          5     THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> NNRTI
NNRTI IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).
```

```
=> s NNRTI
           824 NNRTI
           647 NNRTIS
L9        1162 NNRTI
                (NNRTI OR NNRTIS)

=> s l9 with tenofovir
MISSING OPERATOR L9 WITH
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l9 and tenofovir
          1079 TENOFOVIR
L10         88 L9 AND TENOFOVIR

=> s l10 and py<=2004
      25113462 PY<=2004
L11         29 L10 AND PY<=2004

=> s L11 and combination
        572125 COMBINATION
        127477 COMBINATIONS
        671052 COMBINATION
                (COMBINATION OR COMBINATIONS)
L12          7 L11 AND COMBINATION

=> d l12 1-7 ibib ab

L12  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2005:1081801  CAPLUS
DOCUMENT NUMBER:         144:224
TITLE:                   Virological outcome of tenofovir plus
                         abacavir-based regimens in previously HIV suppressed
                         patients (recover study)
AUTHOR(S):               Moreno, S.; Elias, M. J. Perez; Terron, J. A.; Antela,
                         A.; Domingo, P.; Ribera, E.; Palacios, R.; Ocampo, A.;
                         Quero, J. Hernandez; Barros, C.; Arazo, P.; Carmena,
                         J.; Herranz, C. R.; Casado, J. L.; Sanchez de la Rosa,
                         R.
CORPORATE SOURCE:        The Recovery Study Team, Hospital Ramon y Cajal,
                         Madrid, Spain
SOURCE:                  International AIDS Conference, 15th, Bangkok,
                         Thailand, July 11-16, 2004 (2004),
                         E710C0555/227-E710C0555/232.  Monduzzi Editore:
                         Bologna, Italy.
                         CODEN: 69HFOX; ISBN: 88-7587-065-9
DOCUMENT TYPE:           Conference; (computer optical disk)
LANGUAGE:                English
AB   We have been conducting a study to identify the most frequent NRTI associated
     toxicities causing withdrawal from that drug.  All patients with sustained
     viral load suppression when switching to any TDF+ABC-based regimens were
     subsequently analyzed.  We have available data of the first 83 patients
     treated with TDF+ABC based-regimens who have reached 24w in one of the
     following regimens: TDF + ABC+ NRTI (n=29), TDF + ABC + NNRTI
     (n=25), TDF + ABC + PIs (rtv boosted or not) (n=20) and TDF + ABC + NRTI +
     PI or NNRTI (n=9).  After 24w 84% (ITT) of these patients
     remained suppressed.  Virol. success across the different
     combinations was: TDF + ABC + NRTI (72%) TDF + ABC + NNRTI
     (96%); TDF + ABC + PI (rtv boosted or not) (90%); TDF + ABC + NRTI + PI or
     NNRTI (89%).  We concluded that in heavily pretreated patients
     with suppressed viremia, NRTI + TDF + ABC-based regimen showed lower
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efficacy than PI or NNRTI-based combinations.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1079564 CAPLUS
DOCUMENT NUMBER: 142:232412
TITLE: CADA, a novel CD4-targeted HIV inhibitor, is synergistic with various anti-HIV drugs in vitro
AUTHOR(S): Vermeire, Kurt; Princen, Katrien; Hatse, Sigrid; de Clercq, Erik; Dey, Kaka; Bell, Thomas W.; Schols, Dominique
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: AIDS (London, United Kingdom) (2004), 18(16), 2115-2125
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To evaluate the anti-HIV-1 activity of the cyclotriazadisulfonamide CADA against primary isolates in vitro and the combination of CADA with approved anti-HIV drugs for potential synergy. Methods: Peripheral blood mononuclear cells (PBMC) were treated with CADA and infected with 16 different clin. isolates. After 8 days of infection, the median inhibitory concentration (IC50) was calculated from the p24 viral antigen content in the supernatant. MT-4 cells were infected with HIV-1NL4.3 and then cultured with CADA or other antiretroviral drugs (i.e., several reverse transcriptase, protease and entry inhibitors), alone and in combination. After 4 days, IC50 was determined for the various drugs in replicate assays. Anal. of combined effects was performed using the median effect principle (CalcuSyn; Biosoft). Results: The entry inhibitor CADA exerted a potent and consistent anti-HIV-1 activity against a wide range of R5, R5/X4 and X4 primary isolates in PBMC. From the two-drug studies, combination indexes showed synergy between CADA and reverse transcriptase inhibitors (zidovudine, stavudine, lamivudine, zalcitabine, didanosine, abacavir, tenofovir, nevirapine, delavirdine and efavirenz), and protease inhibitors (lopinavir, saquinavir, indinavir, nelfinavir, amprenavir and ritonavir). In addition, the combination of CADA with the gp41 fusion inhibitor T-20 (enfuvirtide), the CXCR4 antagonist AMD3100 and the gp120-specific interacting plant lectins from Galanthus nivalis (GNA) and Hippeastrum hybrid (HHA) also resulted in a synergistic inhibition. Conclusions: Compds. that can specifically downmodulate the CD4 receptor in PBMC have broad-spectrum anti-HIV activity against primary isolates and act synergistically when used in conjunction with currently available antiretroviral drugs. They deserve further study as potential candidate anti-HIV drugs.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:682819 CAPLUS
DOCUMENT NUMBER: 142:168540
TITLE: New Nucleoside/Nucleotide Backbone Options: A Review of Recent Studies
AUTHOR(S): Ruane, Peter J.; DeJesus, Edwin
CORPORATE SOURCE: West Hollywood, CA, USA
SOURCE: JAIDS, Journal of Acquired Immune Deficiency Syndromes (2004), 37(Suppl. 1), S21-S29

CODEN: JJASFJ; ISSN: 1525-4135
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) class continues to serve as an important component of the standard of care for HIV infection. Combinations of dual NRTIs/NtRTIs with protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) remain the most commonly used regimens in clin. practice. In recent years, clin. outcomes data on previously novel NRTI/NtRTI backbone combinations have provided clinicians with new options to address potency, tolerability, and convenience of antiretroviral therapy. However, the tolerability, drug-drug interactions, and resistance profiles of specific regimens using new NRTI/NtRTI combinations must be weighed against the needs and preferences of individual patients. This review summarizes recent efficacy and safety data on emerging NRTI/NtRTI combination backbones, including tenofovir DF (TDF) with lamivudine (3TC), abacavir with 3TC, didanosine (ddI) with 3TC, ddI with emtricitabine (FTC), and TDF with FTC.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:469918 CAPLUS
DOCUMENT NUMBER: 141:46661
TITLE: Primer unblocking by HIV-1 reverse transcriptase and resistance to nucleoside RT inhibitors (NRTIs)
AUTHOR(S): Goldschmidt, Valerie; Marquet, Roland
CORPORATE SOURCE: IBMC, Unite Propre de Recherche 9002 du CNRS conventionnee a l'Universite Louis Pasteur, Strasbourg, 67084, Fr.
SOURCE: International Journal of Biochemistry & Cell Biology (2004), 36(9), 1687-1705
CODEN: IJBBFU; ISSN: 1357-2725
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. During zidovudine and stavudine treatment, HIV-1 selects several mutations (thymidine-associated mutations, TAMs) in the reverse transcriptase gene that confer high- and moderate-levels of resistance, resp., to these nucleoside reverse transcriptase inhibitors (NRTIs). The mechanism of the resistance provided by these mutations has long remained elusive. However, recent data showed that ATP-phosphorolysis, a reaction analogous to pyrophosphorolysis (the reverse of the nucleotide incorporation reaction) in which ATP is the pyrophosphate donor, is central to this mechanism by allowing repair of the chain-terminated primer. A detailed structural and mechanistic model accounting for the specificity of the ATP-phosphorolysis and its inhibition by the next complementary nucleotide is now available. In the context of multiresistant viruses, the TAMs are also associated with resistance to abacavir, and to a lesser extent to didanosine, zalcitabine and tenofovir. When associated with the TAMs, a dipeptide insertion in the fingers of reverse transcriptase increases the ATP-phosphorolysis of most chain terminators, stressing the increasing importance of this mechanism. However, some non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit this process. In addition, point mutations conferring resistance to NNRTIs (Y181C and L100I) or NRTIs (K65R, L74V, and M184V) partially resensitize the resistant viruses to AZT by inhibiting ATP-phosphorolysis. These findings allow rationalizing the benefic effects of some drug combinations and should contribute

to improve drug cocktails. The development of NRTIs that would not allow the ATP-mediated excision to take place should prove beneficial for future treatments, even though high-level resistance to multiple NRTIs can ultimately develop in the absence of any significant primer unblocking.

REFERENCE COUNT: 156 THERE ARE 156 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:403774 CAPLUS
DOCUMENT NUMBER: 141:374319
TITLE: Molecular targets and compounds for anti-HIV therapy
AUTHOR(S): De Clercq, E.
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Biomedical and Health Research (2002), 55(Drug Discovery and Design), 272-278
CODEN: BIHREN; ISSN: 0929-6743
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Virtually all the compds. that are currently used, or under advanced clin. trial, for the treatment of HIV infections, belong to one of the following classes: (i) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs): i.e., zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir (ABC), emtricitabine [(-)FTC], tenofovir (PMPA) disoproxil fumarate; (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs): i.e., nevirapine, delavirdine, efavirenz, emivirine (MKC-442); and (iii) protease inhibitors (PIs): i.e., saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, and lopinavir. In addition to the reverse transcriptase and protease step, various other events in the HIV replicative cycle are potential targets for chemotherapeutic intervention: (i) viral adsorption, through binding to the viral envelope glycoprotein gp120 (polysulfates, polysulfonates, polyoxometalates, zintevir, neg. charged albumins, cosalane analogs); (ii) viral entry, through blockade of the viral coreceptors CXCR4 and CCR5 [bicyclams (i.e. AMD3100), polyphemusins (T22), TAK-779, MIP-1α LD78β isoform]; (iii) virus-cell fusion, through binding to the viral glycoprotein gp41 [T-20 (DP-178), T-1249 (DP-107), siamycins, betulinic acid derivs.]; (iv) viral assembly and disassembly, through NCp7 zinc finger-targeted agents [2,2'-dithiobisbenzamides (DIBAs), azadicarbonamide (ADA) and NCp7 peptide mimics]; (v) proviral DNA integration, through integrase inhibitors such as L-chicoric acid and diketo acids (i.e. L-731,988); (vi) viral mRNA transcription, through inhibitors of the transcription (transactivation) process (fluoroquinolone K-12, Streptomyces product EM2487, temacrazine, CGP64222). Also, in recent,years new NRTIs, NNRTIs and PIs have been developed that possess resp. improved metabolic characteristics (i.e. phosphoramidate and cyclosaligenyl pronucleotides of d4T), or increased activity against NNRTI-resistant HIV strains [second generation NNRTIs, such as capravirine and the novel quinoxaline, quinazolinone, Ph Et thiazoly-lthiourea (PETT) and emivirine (MKC-442) analogs], or, as in the case of PIs, a different, non-peptidic scaffold [i.e. cyclic urea (DMP 450), 4-hydroxy-2-pyrone (tipranavir)]. Given the multitude of mol. targets with which anti-HIV agents can interact, one should be cautious in extrapolating from cell-free enzymic assays to the mode of action of these agents in intact cells. A number of compds. (i.e. zintevir and L-chicoric acid, on the one hand, and CGP64222 on the other hand) have recently been found to interact with virus-cell binding and viral entry in contrast to their proposed modes of action targeted at the integrase and transactivation process, resp.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:363049 CAPLUS
DOCUMENT NUMBER: 142:15
TITLE: Antiviral drugs in current clinical use
AUTHOR(S): De Clercq, Erik
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Journal of Clinical Virology (2004), 30(2), 115-133
CODEN: JCVIFB; ISSN: 1386-6532
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The current armamentarium for the chemotherapy of viral infections consists of 37 licensed antiviral drugs. For the treatment of human immunodeficiency virus (HIV) infections, 19 compds. have been formally approved: (i) the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine; (ii) the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir disoproxil fumarate; (iii) the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine and efavirenz; (iv) the protease inhibitors saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir (combined with ritonavir at a 4/1 ratio) and atazanavir; and the viral entry inhibitor enfuvirtide. For the treatment of chronic hepatitis B virus (HBV) infections, lamivudine as well as adefovir dipivoxil have been approved. Among the anti-herpesvirus agents, acyclovir, valaciclovir, penciclovir (when applied topically), famciclovir, idoxuridine and trifluridine (both applied topically) as well as brivudin are used in the treatment of herpes simplex virus (HSV) and/or varicella-zoster virus (VZV) infections; and ganciclovir, valganciclovir, foscarnet, cidofovir and fomivirsen (the latter upon intravitreal injection) have proven useful in the treatment of cytomegalovirus (CMV) infections in immunosuppressed patients (i.e. AIDS patients with CMV retinitis). Following amantadine and rimantadine, the neuraminidase inhibitors zanamivir and oseltamivir have recently become available for the therapy (and prophylaxis) of influenza virus infections. Ribavirin has been used (topically, as aerosol) in the treatment of respiratory syncytial virus (RSV) infections, and the combination of ribavirin with (pegylated) interferon-alpha has received increased acceptance for the treatment of hepatitis C virus (HCV) infections.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:95024 CAPLUS
DOCUMENT NUMBER: 141:218332
TITLE: HIV Type 1 Genotypic Resistance in a Clinical Database Correlates with Antiretroviral Utilization
AUTHOR(S): Kagan, Ron; Winters, Mark; Merigan, Thomas; Heseltine, Peter
CORPORATE SOURCE: Department of Infectious Diseases, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, 92690, USA
SOURCE: AIDS Research and Human Retroviruses (2004), 20(1), 1-9
CODEN: ARHRE7; ISSN: 0889-2229
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB We established a database of HIV-1 reverse transcriptase (RT) and protease (PR) sequences and mutations to monitor the prevalence of antiretroviral drug resistance and mutational patterns in clin. samples submitted for testing to a major U.S. reference laboratory At the end of 1998, 80% of the clin. samples tested harbored HIV strains with genotypically predicted resistance to at least one antiretroviral (ARV) drug. By the third quarter of 2002, the frequency of genotypically predicted resistance declined to 65% of samples tested. The prevalence of both PR and nucleoside RT inhibitor resistance declined over this period, while an increase in resistance to non-nucleoside RT inhibitors was found. These genotypic results strongly correlated with a nationwide decrease in the prescription of PR and nucleoside RT inhibitors, and an increase in the prescription of non-nucleoside RT inhibitors over the time period. The increased number of strains that were genotypically sensitive to all classes of ARV probably indicates an increase in genotypic assay use in ARV-naive individuals, however, the trends and correlations in this data set were similar when evaluated after vve strains. Continued monitoring of ARV resistance prevalence, patterns, and utilization trends in clin. databases provides insight into the evolving relationship between clin. practice and ARV resistance.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 14:33:35 ON 04 NOV 2008)

FILE 'CAPLUS' ENTERED AT 14:40:02 ON 04 NOV 2008

L1 4321 S (NNRTI OR "NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS" O
L2 432 S L1 AND TENOFOVIR
L3 102 S L2 AND PY<=2004
L4 0 S L3 AND TCM278
L5 38 S L3 AND COMBINATION

FILE 'STNGUIDE' ENTERED AT 14:45:49 ON 04 NOV 2008

FILE 'CAPLUS' ENTERED AT 14:57:26 ON 04 NOV 2008

L6 0 S TCM278
L7 1 S L3 AND TMC278
L8 16 S TMC278
L9 1162 S NNRTI
L10 88 S L9 AND TENOFOVIR
L11 29 S L10 AND PY<=2004
L12 7 S L11 AND COMBINATION